ARCHIVES OF DISEASE IN CHILDHOOD

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SIR THOMAS BARLOW BIRTHDAY NUMBER

CONTENTS

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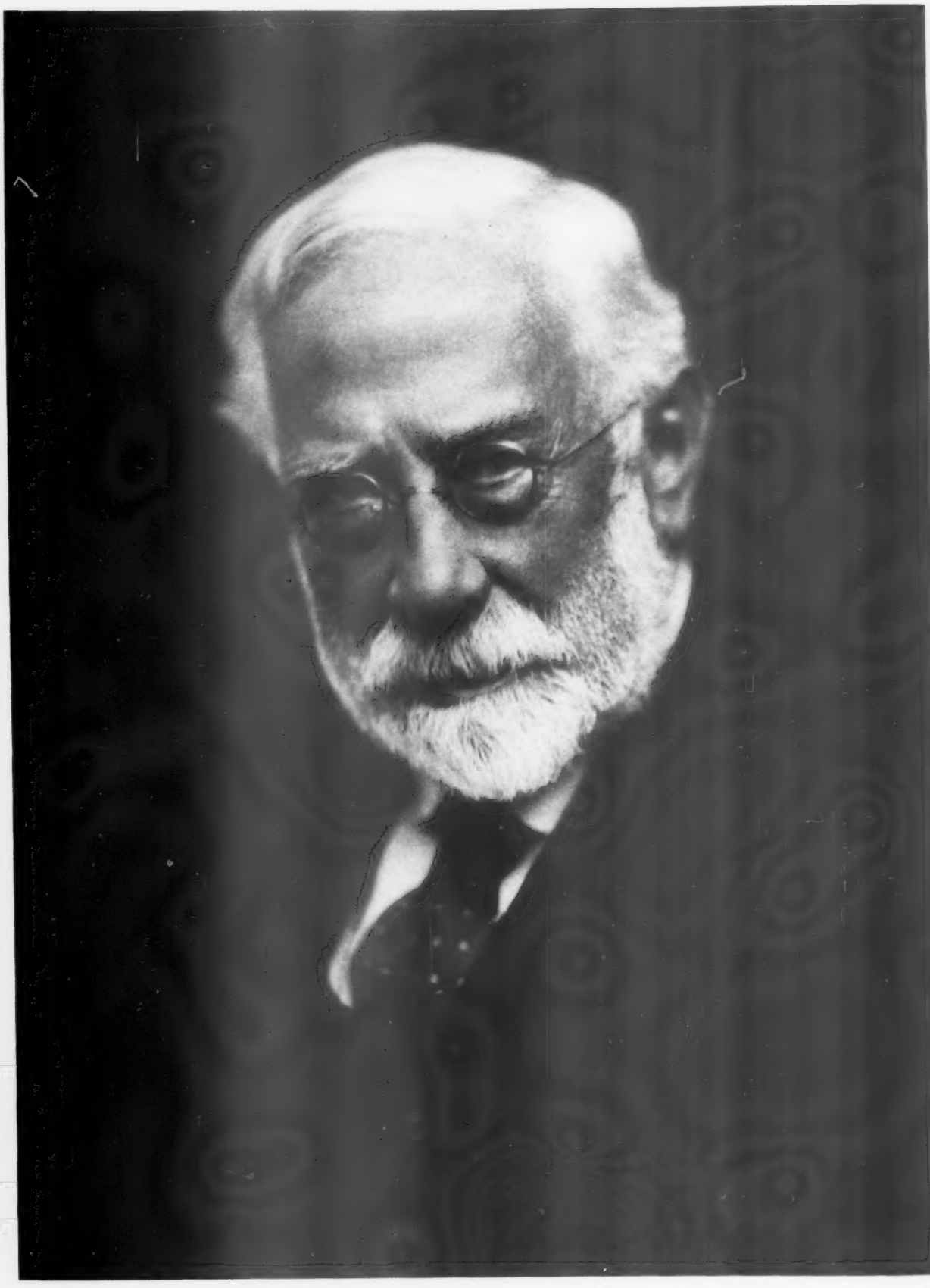

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To

SIR THOMAS BARLOW, Bart.,

K.C.V.O., F.R.S., M.D.,

Born September 4th, 1845

On the occasion of his

90TH BIRTHDAY.

INTRODUCTION

BY

The Rt. Hon. LORD HORDER, K.C.V.O., M.D., F.R.C.P.,
Physician to St. Bartholomew's Hospital.

To introduce these essays, written in honour of the man who is so easily, and so notably, the doyen of British medicine, is a very pleasant duty. That the writer's clinical alma mater is not Barlow's has not biassed the Editor unfavourably. What has had more weight with him is his knowledge that the relations of teacher and pupil have existed for forty years and that they have engendered a degree of respect and affection in the disciple which have amounted almost to adoration.

But of Barlow it might be said more truly perhaps than of any of his contemporaries, that he is of no one school, but of all. This is to say that he has been too great to be parochialized. As to the emotion excited in the younger man by the older, the same may surely be said of all the contributors of this volume, as also of hundreds of others who have come under the sway of that genially virile personality.

An illustrated magazine recently published an article upon medical men who doctored members of the royal household. The photograph which accompanied the paragraph referring to Sir Thomas Barlow was that of his distinguished son. The error has a symbolism which is both true and beautiful, for the vigour of robust manhood has remained with Barlow much longer than it is wont to do with men of his age. Though it is many years since his colleagues have been deprived of that wealth of experience, sound judgment and cheery helpfulness they invariably got from him, he has retained an active interest in many affairs that have as their object human betterment in general and the welfare of the medical profession in particular. He has continued until now to infuse vitality into every institution and movement in which he has taken a part.

At the time Barlow was making his most important contributions to medical knowledge his contemporaries included, in this country, such stalwarts as Hughlings Jackson, Gowers, Hutchinson, Gee and Cheadle; in France, Charcot, Houchard and Pierre Marie. Though his influence on general medicine was great, it is in the special sphere of diseases of children that his main efforts lay and it is here that his name will live as long as the history of medicine continues to be written. It is very appropriate, therefore, that this Birthday Volume should contain a symposium which deals with various aspects of the disease which Barlow discovered. It illustrates the enormous field that such a discovery laid open as well as the extent of the penetration into it which his pupils and followers have achieved.

This book is presented to Sir Thomas Barlow with admiration and affection, with sincere congratulations upon his ninetieth birthday, and with fervent hopes that he may remain amongst them a long time yet to stimulate and to inspire.

INFANTILE SCURVY: ITS HISTORY

BY

G. F. STILL, M.D., F.R.C.P.
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As early as the sixteenth century and still more in the seventeenth century the clinical picture of scurvy was acquring a distinctness which it had never had before in the minds of medical men. In 1534 Euricius Cordus, a physician of eminence, as well as a poet, had written on the scurvy, and five years later the Professor of Medicine (and of Greek!) at the University of Ingolstadt, Johannes Agricola, devoted part of his writings to this subject. There is no reason to assume that scurvy came into existence at that time; indeed, it is quite certain that it must have occurred as soon as man discovered ways of subsisting without fresh meat and milk and the fruits of the earth, and especially when his journeyings by sea became extended so that he was more dependent upon long-preserved foods. Writers in the seventeenth century—which was particularly prolific in works on scurvy—still anxious to maintain the Hippocratic tradition, were at pains to show that Hippocrates had referred to scurvy, without naming it, as an affection of the gums or mouth associated with enlargement of the spleen, and that Galen, more explicitly, had described it under the names of στομακάκη and σκελοτύρβη, by emphasizing the oral manifestations and the weakness and difficulty in walking due to that affection: and they had no doubt that Pliny had meant scurvy when he described (Nat. Hist. Bk. xxv., c. 6) how the soldiers of Germanicus, campaigning on the Rhine, suffered, after the campaign had lasted two years, with loosening of the teeth and weakness in the limbs, and how a remedy was discovered for this in eating a plant called Herba Britannica, thought by modern writers to be the Inula Britannica of Linnaeus, or possibly some variety of sorrel. I have searched amongst many of the early writings on scurvy for any mention of its occurrence in infants or in children. It is not surprising that writers dealing with the disease, as many did, almost exclusively as an affection of soldiers and sailors, should make no mention of children. Gradually it came to be recognized that scurvy occurred also amongst the civilian population on land, but even then there is little separate mention of its occurrence in children. This can hardly be because it did not occur in them, for although breast feeding was prolonged, in most countries in the sixteenth and seventeenth centuries, to at least two years of age, and no doubt to some extent reduced the chance of scurvy in infancy, it must be remembered that the mother or foster-mother herself must often have been suffering from lack of fresh food, so that her milk must have lacked antiscorbutic value. The great factor in the wide prevalence of scurvy before the end of the

eighteenth century was the absence of fresh food during the winter. Of all the antiscorbutic foods which reduced the incidence of scurvy in later times, by far the most important, especially as being available throughout the winter, was the potato. Introduced into this country by Sir Walter Raleigh in 1585, it was still only a luxury in 1626, and, although the Royal Society urged its cultivation in 1663, it was not until the latter part of the eighteenth century that it began to be cultivated on a large scale. For the most part the population, especially the poorer sort, subsisted through the winter upon foods very poor in antiscorbutic value; in Belgium and in Spain the potato came into use a little earlier.

The essential relation of scurvy to diet, however, was unknown when the physicians of the sixteenth and seventeenth centuries tried impotently to mitigate this terrible disease, which, as they imply, even if they do not state, affected children and adults alike. A writer in 1609, Schenk, says that scurvy is sometimes found in several members of a family, and adds significantly, 'Partim quod eodem victu sint usi,' i.e., because they have lived on the same diet, and apart from referring to 'pueri' as affected by it, he mentions casually of a particular form of supposed antiscorbutic treatment, that he had used it for a tender infant, 'tenello infanti.'

Probably the scanty reference to the occurrence of scurvy in infancy and childhood is due chiefly to the fact that these early writers described the disease without distinctions of age, indeed, some of their statements imply this, e.g., Balthazar Bruner in 1658, in a treatise, De Scorbuto, says, 'Saepe totas familias invadit,' and mentions that in children the oral symptoms were more frequent than the limb symptoms; and another writer of the same date, Henricus Brucaeus, says that it 'attacks persons of any age,' 'cujusvis aetatis et sexus.' What wonder if medical men, seeing whole families stricken with the scurvy, concluded that it must be either contagious or inherited if, indeed, they did not, with less logic, attribute it, as Eugalenus did, to the Devil!

It might seem strange that with so near a guess at the truth as was made by Schenk and others, who regarded diet as an important factor, physicians in the sixteenth and even in the seventeenth centuries considered contagion and heredity as possible sources of scurvy; Gregorius Horstius, for instance, at the same date as Schenk, stated that diet was a potent factor in the production of scurvy, and yet goes on to say that children, as a result of heredity become predisposed to scurvy (nativa dispositio scorbutica lienis a parentibus in filios propagatur), and that infants might contract the disease from kissing. Similar views were expressed by Gideon Harvey, physician to Charles II, in 1675, in a verbose and tedious treatise on 'The Disease of London, or a new Discovery of the Scorvey,' where he seems to imply its occurrence in infants. He says it is contracted 'by means (1) of the Semen of the Parent and its plastic Faculty; (2) of the Uterin Blood; (3) of the Milk assuged by the Infant; (4) of the Contact of the Lips of the Mouth

and ambient Skin of the Body, whereby the Scorbutic μιασμα is transferred to the Child by being Kissed or Hugged by the Parents and lying by them in Bed.' The title of his treatise is interesting as suggesting that 'the Scorvey' was common in London at that time.

In the study of medical history, however, there is a fallacy always to be remembered, that until the clinical and pathological manifestations of a disease have become so clearly defined that its differentiation from other diseases is reasonably reliable, a name may cover morbid entities which are entirely distinct from one another. Already in 1686 Thomas Sydenham,* with his clinical acumen, had perceived that the name of scurvy was being applied to conditions which were essentially different, and instances gout, rheumatism, and the vague initial symptoms of various diseases. Avowedly syphilis and scurvy had been thought to be akin, and it is easy to see how infantile syphilis might have been and almost certainly was, confused with infantile scurvy. Purpura also was a source of confusion; Martin Lister,† in 1694, describes in some detail four cases of 'Scorbutus' in children aged respectively 5, 10, 6 and 8 years, but his description suggests that they were not really cases of scurvy, but of what would now be called primary purpura, one of them a fatal purpura hæmorrhagica.

The first clear description of Infantile Scurvy was given by Francis Glisson in his De Rachitide in 1650.

> The Scurvy complicated with this Affect (rickets) hath these signs :—
>
> (1) They that labour under this affect do impatiently endure Purgations; but they who are only affected with the Rachites do easily tolerate the same.
>
> (2) They are much offended with violent exercises, neither can they at all endure them. But although in this affect alone ther be a kind of slothfulness and aversation from exercise, yet exercise doth not so manifestly, at least not altogether so manifestly hurt them as when the Scurvy is conjoyned with Rachites.
>
> (3) Upon any concitated and vehement motion they draw not breath without much difficulty, they are vexed with divers pains running through their Joynts and these they give warning of by their crying, the motion of the Puls is frequent and unequal, and sometimes they are troubled with a Palpitation of the Heart or threatened with a lypothymie, which Affects are for the most part soon mitigated or altogether apeased by laying them down to the rest.
>
> (4) Tumors do not uncommonly appear in the Gums.
>
> (5) The urin upon the absence of the accustomed Feaver is much more intens and encreased.
>
> Such was Glisson's description of Infantile Scurvy; which he says 'is sometimes conjoyned with this Affect (the rickets). It is either hereditary or perhaps in so tender a constitution contracted by infection, or lastly, it is produced from the indiscreet and

* *Observationes Medicae*, 1686.
† *Sex exercitationes Medicinales*, 1694.

> erroneous Regiment of the Infant, and chiefly from the inclemency of the Ayr and Climat where the Child is educated.* For it scarce holdeth any greater commerce with this Diseas then with other Diseases of longer continuance, wherein after the same manner the Blood in time contracteth, yet it must be granted, that this Affect doth somewhat the more dispose to the Scurvy in regard of the want of motion and exercise.'

It seems strange that Glisson's recognition of scurvy in association with rickets remained a dead letter for 200 years. Glisson was obviously writing from shrewd clinical observation; moreover, he recognized what was not fully appreciated until Barlow stressed the point in his communication to the Medico-Chirurgical Society in March, 1883, that rickets is no essential concomitant of infantile scurvy.

Even such careful clinical observers of diseases of infancy and childhood as George Armstrong, Heberden and Underwood make no mention of the condition which Glisson had described so faithfully. Perhaps in some degree this omission was due to the gradual diminution in the frequency of scurvy which must have occurred as the antiscorbutic value of vegetables and fruit came to be more and more recognized, and especially when potatoes came to be more generally available. As early as 1646 a Jesuit monk, Baptiste Ferrari, had published at Rome a work on the cultivation and use of the orange, and a German writer, John Drawitz, in 1647, had reported that sailors were 'speedily and effectually cured of the Scurvy by eating oranges,' and in 1694 Martin Lister (loc. cit) wrote that 'the chief remedies for this disease are teaspoonfuls of orange-juice and lemon-juice.' In 1778, De Mertans, in a paper communicated to the Royal Society, describing the terrible incidence of scurvy amongst the children in a Foundling institution in St. Petersburg, recognized not only the antiscorbutic value of vegetables, but its diminution after cooking. 'I am convinced,' he says, 'that all the greens used in our kitchens are much more antiscorbutic when they are raw than after they have been boiled in water or have gone through any other preparation by fire.' He states particularly that none of the children 'were ever seized with the scurvy under two years old'; in this connection it is noteworthy that some at least of the younger children were boarded out with foster nurses, 'La plus part des petits à la mamelle étoient en nourrice à la campagne.' Even Lind, in his exhaustive and masterly work on the scurvy in 1754, has no mention of its occurrence in infants; the only instance mentioned in a child is in a boy aged 10 years. Lind, in his very full bibliography, does not include the name of Glisson.

With the increasing understanding of the essentials in the prevention and treatment of scurvy the disease must have become less prevalent. In the latter half of the eighteenth and earlier half of the nineteenth centuries the evil day of dried patent foods for infants had not yet dawned, so that the most potent cause of infantile scurvy in the latter

* 'Educated' is of course used here in its literal sense of 'brought up,' not of scholastic training.

half of the nineteenth century was not yet in operation, and this disease must, therefore, have been seen much less frequently in infants than in the time of Glisson. He had made two important observations with regard to infantile scurvy: (1) that it was sometimes associated with the rickets; (2) that the rickets bore no essential relation to it. These were ignored or forgotten, and later writers fell into confusion on the relationship. In 1795 S. T. Soemmering* propounds the view that 'Scurvy in adults is akin to, if not identical with, the disease which they call Rickets in infants, the one disease differs from the other exactly in proportion as the infantile body differs from the adult'; he regarded rickets and scurvy as one and the same disease, merely modified by age. A still more retrograde error was put forward by Antoine Portal† in his work on Rickets, 1797, where he regards rickets as a symptom of various diseases, such as gout and syphilis, and has a section, 'Du Rachitisme occasionné par le vice Scorbutique,' in which he describes a case which may have been scurvy in a girl of 10 years, but in which he gives no proof whatever of the rickets which he considers to have accompanied it. Montfalcon, who quotes this case in the Dict. des Sciences Med., 1820, says 'On a vu dans d'autres cas, assez rares toutefois, une pareille complication du rachitis et du scorbut,' but gives no instances.

By 1859 scurvy had so far receded from the foreground of medical perspective that not only had Glisson's observations on infantile scurvy been forgotten, but even the possibility of scurvy being associated with rickets was regarded as something unknown. In that year Prof. Möller‡ reported three cases of 'Acute Rickets,' and whilst denying that ordinary rickets was inflammatory, admitted that these acute cases reminded one decidedly of an 'osteitis.' In 1862 he recorded more fully two cases in children, aged respectively 14 months and 21 months, one of which died and showed a subdural haemorrhage. In the other case the purple swelling of the gums specially attracted his attention, and he noted, 'Sehr bald nahm es eine völlig scorbutartige Beschaffenheit an.' Even then, with this resemblance before him, he did not recognize that it was actually scurvy, and after months of unsuccessful treatment, 'endlich, wegen der Aehnlichkeit mit dem Scorbut, Citronensaft und frische Gemüse versucht, alles ohne den mindesten Erfolg.' And then comes warm weather and the child's recovery is attributed to fresh air! The lemon juice and the fresh vegetables get no credit; and Möller concludes that the acuteness of symptoms in such cases is due to abnormal rapidity of growth in the bones, and that the resemblance to scurvy is merely external and symptomatic. 'Was ubrigens die durch solche Knochenblutungen entstehende Aehnlichkeit mit Scorbut betrifft . . . so halte ich sie nur für eine rein äusserliche symptomatische.'

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* *De morbis vasorum absorbentium*, 1795.

† *Observations sur la Nature et sur le traitement du Rachitisme*, Paris, 1797.

‡ *Konigsberger Med. Jahrbücher*, I, 1859, and III, 1862.

It seems hardly appropriate that, as sometimes happens, infantile scurvy should be called 'die Möller-Barlowsche Krankheit,' for Möller failed to recognize the scorbutic nature of the disease, the very point which Barlow's investigations established. After Möller, cases of this affection continued to be described as 'Acute Rickets,' with no inkling of scurvy, until Ingerslev* in 1871 recorded a case of scurvy in an infant aged 15 months. Ingerslev has not received the credit he deserves: he not only gave a graphic description of this case, but he was quite clear as to its being scurvy: 'det var dog tydeligt en skorbutisk Tilstand,' he says; and unlike other writers before and after him, he makes no confusion between it and rickets, indeed he does not even mention rickets. He points out that good hygiene was powerless to prevent it in presence of faulty diet: lack of vegetables was the fault, 'det just er Savnet af Vegetabilier som giver Anleding til Skorbug,' but he thought that vegetables might be antiscorbutic rather by affording a mixed diet than by any special virtue.

In 1876 the nature of this affection was still in doubt in this country. Sir Thomas Smith had under his care at the Children's Hospital, Great Ormond Street, a fatal case, and it was at Barlow's suggestion that the condition found post mortem was called 'Haemorrhagic periostitis,' a term which Barlow himself later condemned as inappropriate. In November, 1878, and in July, 1882, Dr. W. B. Cheadle described cases under his care with full recognition of their scorbutic character, and that they were instances of 'Scurvy supervening on rickets.' He propounded the deficiency origin of the disease: 'There is an invariable factor. . . . This essential factor it has been proved over and over again is the absence of certain elements in food.' In 1881, however, so acute a clinician as Gee, then colleague of Dr. Cheadle, at Great Ormond Street, still failed to recognize these cases as scurvy, for he reported five cases under the name of 'Osteal or periosteal cachexia,' observed between 1878 and 1880. 'Quandoque bonus dormitat Homerus'!

In 1883 the nature of this affection was finally settled by pathological evidence brought forward by Barlow, then Assistant Physician to the Children's Hospital, Great Ormond Street. His paper 'On cases described as Acute Rickets, which are probably a combination of Scurvy and Rickets, the Scurvy being an essential and the Rickets a variable element,' was read before the Medico-Chirurgical Society of London† and accompanied by an exhibition of pathological specimens illustrating the condition in three fatal cases, on March 27, 1883. Between 1883 and 1894, when Barlow delivered his Bradshaw Lecture on 'Infantile Scurvy and its relation to Rickets,' he had had 33 cases under his care, and was able to add some important clinical details to the picture of infantile scurvy, giving a completeness to it which has left very little to be added by subsequent observers. The pathology of scurvy remained an unsolved problem. Barlow stressed, what earlier observers had already recognized,

* Et Tilfaelde af skorbug hos et Baru. Hospitals—Tidende, Aug. 2. 1871.
† See p. 223 for this original paper.

the importance of fresh food in the prevention and treatment of scurvy, but chemists were searching in vain for the *causa causans* of scurvy. It was only when Holst and Frölich in 1912* first showed that animals could be rendered scorbutic (they used guinea pigs) that advance became possible in the investigation of the causal factors in scurvy, and since that time a host of observers have been at work determining experimentally, by tests upon animals susceptible to scurvy, the degree of scorbuticity of various foods, the presence or absence of the antiscorbutic factor in particular foods, and the conditions which affect its potency. Following the lead of Sir Gowland Hopkins, it had become usual to name the particular deficiency which rendered a food scorbutic, deficiency of vitamin C, and various facts had been ascertained with regard to this hypothetical vitamin C, but still it remained unfound, until, in 1928, Györgyi† isolated a crystalline substance from the adrenal cortex of the ox, and also from orange and from cabbage, to which he gave the name hexuronic acid: a substance with powerful antiscorbutic activity. Further chemical investigations were made by Cox, Hirst and Reynolds in 1932, leading to a change of name. The substance was re-named ' ascorbic acid,' or, as some Continental writers name it, ' ascorbinic acid.'

This chemical substance, ascorbic acid, is now very generally accepted as the essential antiscorbutic factor. Its artificial synthesis seems already to have become an accomplished fact, which may have some practical bearing upon the prevention of infantile scurvy in the future.

Valuable and interesting as these laboratory investigations of the last few years have been, it is not to them that we can attribute the decrease of suffering and also of mortality from infantile scurvy which is so evident in the past half-century. This is due to the demonstration of the scorbutic nature of the disease by Sir Thomas Barlow, and the clear description of its clinical features by him and by Dr. W. B. Cheadle, making its recognition gradually more universal; their insistence at the same time upon its amenability to one treatment, and one only, the administration of the element deficient in the scurvy-producing diet, by giving fruit juice, potato, and fresh meat juice, has been the means of preventing and relieving a large amount of infant-suffering.

One point which must strike everyone familiar with the disease, as seen in recent years, is the discrepancy between the average age of the cases recorded 50 or 60 years ago, and that of cases seen to-day. In that earlier period the cases recorded were mostly over a year old. Cheadle's three cases were respectively 16 months, 16 months, and 3 years old. Twenty out of Barlow's 35 collected cases were over a year old, whereas nowadays and, indeed, within the past twenty years, a case over a year old is quite the exception, the large majority being between six months and twelve months old. The meaning of this—as a study of those older cases shows—is that the disease, thanks chiefly to the writings and

* Holst, A., & Frölich, T., *Zeitschr. f. Hyg. und Infect.*, 1912, 72, 1.
† A. Szent Györgyi, *Biochem. Journ.*, 1928, XXII, 1387.

teaching of Sir Thomas Barlow, is diagnosed so much earlier, and the feeding corrected, on the lines emphasized by him, so much earlier, that the infant is saved weeks and months of the terrible suffering which an unrecognized case of infantile scurvy undergoes. The point stressed by Barlow, that scurvy is the essential and rickets only a variable manifestation in these cases, was not fully recognized for several years. The misleading term, 'scurvy-rickets,' is sometimes heard even to-day, and was in common use thirty years ago, perpetuating haziness of ideas as to the pathology and treatment of a condition which, as Glisson recognized, and Barlow finally established, is essentially scorbutic and responds not to antirachitic treatment, but only to antiscorbutic measures.

At the time when Barlow first demonstrated the scorbutic nature of the disease from pathological investigation, the mortality of infantile scurvy in the series of cases which he collected, was 1 in 4.5 approximately; as a result of the better understanding of this disease, and its more general and earlier recognition since his investigations were published, the mortality has fallen to about one-fourth of this proportion; in a series of 155 cases, under the present writer's observation, it was almost exactly 1 in 18.

The aim of medicine is not only to reduce mortality, but to reduce suffering, and in this latter respect a splendid contribution was made to medicine by those investigations which gave to infantile scurvy its alternative name, Barlow's Disease.

Dr. CHEADLE AND INFANTILE SCURVY

BY

F. JOHN POYNTON, M.D., F.R.C.P.,

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The writer of this short article has always felt a certain glamour surrounding the lives of the distinguished physicians and surgeons of former days. This becomes less evident among those of our own day possibly because times have greatly changed and possibly because one has grown up alongside them. There is a thrill in the vision of Dr. Fordyce in 1784 working away feverishly in the Honourable Artillery Ground superintending the inflation of Lunardi's balloon with inflammable gas on the occasion of the first aerial journey in this country, doing this in the presence of a crowd of 150,000 spectators crammed into this space and ready enough to be truculent. Dr. Cheadle had around him much of this glamour. A large powerful Yorkshireman of immense tenacity of purpose had he not made the famous North-West Passage by land across Canada with Lord Milton? Many a time the writer, who had the honour of living with him for ten years and standing by him in days of sorrow and suffering, has seen the belt which he had pulled in inch by inch whilst starving on that perilous and famous journey.

Cheadle had seen the splendid and undebased Red Indian and had given a name to a mountain which was later described by Grant in 'Ocean to Ocean' as the 'biceps Parnassus' and Grant named his camp pitched near by this mountain 'Cheadle Camp.' His journey of exploration began on the screw steamer Anglo-Saxon bound from Liverpool to Quebec on June 19, 1862, and on July 2 they steamed up the St. Lawrence to Quebec and thence made their way from the Atlantic to the Pacific. Their intention was to explore a route across Canada through British territory by one of the northern passes in the Rocky Mountains to British Columbia. This journey was described by the explorers in 'The North-West Passage by Land,' the ninth edition of which was published in 1901.

This part of Cheadle's life is alluded to because he told me that in those wanderings he learnt much about adult scurvy, smallpox, starvation, massacres and hair-breadth adventures. He often told me also that when he returned to London and was on the honorary staff of the Hospital for Sick Children, Great Ormond Street, he recognized the scurvy of infants, and that he had known doctors clip the fungating gums of these children in sheer perplexity as to know how to act. Also he impressed upon me the anti-scorbutic principle of his treatment of these cases, insisting that it was a special and not a general alteration in the diet.

It was Cheadle who wrote ' The Rheumatic State in Children ' in which he recorded facts which are almost daily being rediscovered. Yet his contribution to the knowledge of infantile scurvy must I think be the greatest monument to his memory. Charming with patients, he would place his great hand on a child in a way which almost seemed to obliterate the patient, yet that child would call after him ' Doctor Cheagle, doctor Cheagle, I want a sweet ': but no man was more difficult to know for he was both shy and reserved.

It was with this sense of glamour that one reads the opening sentence of his famous clinical lecture on ' Three cases of scurvy supervening on rickets in young children ' published in ' The Lancet ' in the second volume of 1878. He writes: ' The outbreak of scurvy during the late Polar Expedition on which it had so disastrous an influence, has specially associated the disease in the public mind with an Arctic climate.' In those days naval officers still attributed scurvy to extreme cold, prolonged absence of sunlight and severe physical exertion rather than to diet. Cheadle then points out that it occurs in tropical climates and under the full glare of a summer's sun, and proceeds to describe three cases of scurvy in young children of ages from sixteen months to three years. These, he says, had no protracted exposure to great cold, or prolonged absence of sunlight, or again exhausting physical exertion, but they had been strangely dieted. The first child from the sixth to the fourteenth month was not given any milk or meat or potatoes and nothing but oatmeal, rusks and water with a little mutton broth. The second from the thirteenth to the sixteenth month had lived on bread with a little butter and a one-seventh share in a pint of milk together with a patent food. The third had been weaned at two years and then fed for about a year upon bread and butter and tea with occasionally some German sausage and a little brandy and water.

These three cases were examples of rickets and scurvy combined, but of scurvy of such severity that of one case Cheadle writes ' dark red, soft and gelatinous masses protruded from the mouth between the lips and gave the

child the appearance of being engaged in sucking pieces of raw flesh.' After the classical descriptions of the case, which illustrated also the varied though unsuccessful efforts at treatment attempted by doctors who were groping in darkness for the cause, Cheadle writes 'the diet was, however, more than a rickety diet it was a scurvy diet.' The word scurvy is in italics. **This sentence of his is an historic one in English medicine.**

Thinking as it were in print over this infantile scurvy he asks why did these three rickety children out of all the number alone become scorbutic? 'All the number' refers to the rickets which was then so frequent. I believe, he then answers himself, one factor was wanting in all these three cases—potatoes, and he points out that in those days after a child was weaned the poor could not afford meat, but gave the children potatoes and gravy and Dr. Baly had already shown that potatoes were strongly anti-scorbutic or, if this article is to be tinged with modernity, were rich in vitamin C.

Let me rescue from the forest of well-meant but ineffectual methods of treatment one example from the three cases which shows what Cheadle did. His treatment consisted in a full allowance of unboiled milk with mashed potatoes beaten up in milk, raw meat and the juice of two oranges. He gives the description of the recoveries with no boastfulness but as simple records of facts. They were then indeed marvellous recoveries.

This paper, written in 1878, is fine both in its sagacity and simplicity. The children can be seen together with the perplexities, and in simple words the treatment and its results are expressed. It is surprising that there are not found in 'The Lancet' letters and further experiences confirming and praising this masterly article. When we remember the infantile scurvy we saw some thirty years ago coinciding with the influx of patent foods we cannot but read that short paper with reverence and thankfulness.

Cheadle was essentially a clinician. Though busy in practice he would never make appointments in his hospital hours. He would never let his house-physician have a day away from hospital if there was a patient dangerously ill. 'Do not leave a dying man' was his stern command. If fate had been unkind, England might never have had this famous man, for he was to have rowed but for illness in the Cambridge boat that sank in the University race and he could not swim! He was indeed a man of iron, for when nearly seventy years of age he would stay up night after night looking after his beloved wife, then snatch a little sleep after breakfast and work away through the day, sleeping again toward evening before dinner while I kept watch for him.

I have been fortunate in my teachers, but there is one honour I greatly prize: it is that in the well-known 'System of Medicine' by Allbutt and Rolleston, Cheadle coupled my name with his in the article upon infantile scurvy and it is interesting to relate that the radiographic picture in that article was taken from a case over which I had gone astray to be corrected by Sir Thomas Barlow. No doctor young or old can read that paper of Cheadle's written in 1878 and not see in it one of the classics of English medicine.

[*Sir Thomas Barlow's original article on Scurvy reprinted by permission from the Medico-Chirurgical Transactions, London, 1883, LXVI, 159.*]

ON CASES DESCRIBED AS 'ACUTE RICKETS'

WHICH ARE PROBABLY

A COMBINATION OF SCURVY AND RICKETS

The Scurvy being an essential and the Rickets a variable element

BY

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This paper is a contribution to the study of a disease occurring in young children, of which several cases have been recorded in recent German and English literature, but of which hitherto, with one exception, no satisfactory account of the morbid anatomy has been given.

I propose (1) to narrate a typical case, (2) to give an analysis of principal symptoms in the recorded cases and in cases which have come under my own observation, (3) to give the results of post-mortem examinations, and (4) to discuss the etiology and affinities of the disease.

(1) **Typical case.**—A boy, aged fifteen months, was seen in the month of December when the following note describes his condition:—The child has an excessively pale, sallow complexion and is flabby, although he has a moderate covering of fat. There is not sign of nervous disease nor of visceral disease except that the liver is perhaps larger than normal, extending to two fingers' breadth below the thoracic margin as the body lies in the horizontal posture. The bowels have acted one or twice daily; a stool which has been saved is greyish-brown in colour and a little slimy. There has been no vomiting; the tongue is clear. He has cut his two lower incisors; the gums are natural with the exception of a minute erosion in the upper gum opposite the cutting edge of one of the lower teeth. The boy is continually moaning and when approached he screams and still more when he is touched. It is difficult to describe a cry, but it is sufficient to say that in this case it suggested deep-seated pain connected with bones and not brain disease. And it is clear that the dominant symptoms are related to the bones. The boy is rickety; there is some beading of ribs although the thorax is not grooved, his epiphyses are a little enlarged and he has only two teeth, but rickets is not sufficient alone to explain his condition. He lies on his back and scarcely moves the trunk though he frequently turns his head from side to side. Both radii are enlarged at the lower end but the right more so than the left, not only in circumference but in vertical measurement to a slight amount. It,

in fact, suggests a rickety enlargement plus slight thickening extending upwards for perhaps an inch. The child cries wherever he is touched, but the mother has noticed his right wrist notably more tender than the other for a day or two. The skin is pale in the neighbourhood and there is no special heat to be felt. The upper limbs are not bent. The left thigh is kept half flexed. Both the left thigh and leg are slightly swollen so that the contour of the limb is different from natural, assuming in the thigh rather a cylindrical shape. It is of the same colour as the other limb and does not feel hotter than any other part of the body. There is no fluctuation and no sign of effusion in the knee or ankle-joint. The child screams so much that one cannot examine thoroughly, but in spite of his thigh being flexed there does not seem reason to suspect hip-joint trouble.

The epiphyses at the knee and ankle are enlarged.

The right thigh is natural in the sense of there being no swelling. Besides the slight enlargement of epiphyses at the knee there is a tendency to knock-knee on the right side. There is no general swelling of the right leg, but there is a little thickening to be appreciated down the shaft of the right tibia.

There is profuse sweating about the head. There is nothing special about the head itself, except that there is a suspicion of slight thickening of the frontal in front of the fontanelle.

The boy's temperature taken in the rectum is 101° F., 7 p.m.

The history was as follows:—He was the only child of his parents, a young couple in good circumstances, and living in a healthy dwelling. The father is in good health, but the mother is a thin, poorly developed woman, without, however, any history of particular ailments. The child had been born before term and had in its babyhood occasional stuffiness of the nose, but beyond this there was nothing to suggest congenital syphilis, though it is of course difficult to negative its possibility. During the first six weeks he was said to be a vigorous child. For that period he had his mother's milk, then it entirely failed, and from that time until when I saw him he had been quite deprived of fresh food. At first his diet consisted of Robinson's grits and Swiss milk, then of baked flour, then of Nestlé's food, then of Robb's biscuits, then of Liebig's extract, and finally of Swiss milk and saccharated lime water. He had been considered a fairly healthy child. He had not suffered from cough; his bowels had acted not more than twice daily, although the nurse admitted that the evacuations were often unduly offensive; he had had scarcely any vomiting. He had cut his first tooth at twelve months and his second at thirteen months, and these were all he had. His mother admitted that he had been always a pale child, and that although his limbs had been fat they had been thick near the joints, also that he had had much head sweating since he was three months old.

The child had been able to sit up well and stand with assistance at thirteen months old. Five weeks ago he ceased to do either, and then it was noticed that the left leg was swollen especially about the ankle. At this time also he became very peevish and would shriek if he were touched, and often even if he were approached. The boy was then taken to a well-known

bone-setter, who informed the parents that one of the bones of the spine was out, and that an operation was needed to restore it to its proper position. Five days later the said operation was performed, but as the swelling of the left lower limb increased, and the right wrist became swollen and the right hand dropped, and no explanation was forthcoming except the vague suggestion of possible paralysis, a further opinion was desired, and the child's condition was found as above described.

As to diagnosis, it was obvious that the child was the subject of rickets to a moderate degree, and equally obvious that rickets alone was insufficient to explain all his symptoms.

On the ground of certain post mortems which are subsequently detailed, the opinion was formed that in this case there was under the periosteum of the left femur and tibia an effusion of blood, and that the extreme tenseness of the limb was due to blood extravasation in the deeper muscular layers with the serum filtered out into the more superficial parts.

It seemed likely that there was also some slight blood effusion immediately around the shaft of the right tibia and also in the neighbourhood of the junction of shaft and lower epiphyses of the right radius. The view held was that the boy was suffering from the supervention of scurvy on rickets, albeit there was no trace of sponginess of gums. The treatment suggested was to surround the whole of the left lower limb and the right leg with wet compresses which had been thoroughly wrung out. These were to be surrounded with dry cloths rather closely applied, and the compresses were to be changed every two hours.

A complete change was made in the diet. He was ordered daily the juice of a quarter pound of raw beef sweetened a little. He was also to take a pint and a half of cow's milk daily, to which was to be added in his alternate meals at one time a third part of strained gruel, and at another a third part of barley water, and finally two teaspoonfuls of orange juice were to be given daily. It was also ordered that for at least half an hour twice daily the boy's crib should be placed near the fire, and that the window of his room should be opened wide and the door likewise, so that he should have a free play of fresh air around him, precautions being taken about close fitting garments. The directions were most loyally carried out, and in three days there was a notable change in the child. The compresses had certainly been a comfort to the child, so that on the first night of their application he had been a great deal quieter than before. He had taken the fresh food most greedily, and it had agreed with him. His tongue was almost clean and a healthy evacuation had been passed. His rectal temperature had sunk to 99·4°. The left lower limb was less tense and less tender, and the right leg was better.

After this the improvement was progressive. It was several days before any of his urine could be saved, then it was found pale, clear, neutral, free from albumen or excess of phosphates. After about a fortnight the tenseness of the soft parts of the left lower limb had disappeared, and then it was easy to appreciate that the left femur was thicker than the right and in less degree that the left tibia was thicker than the right. The

thickening gradually diminished, but even at the end of six weeks a slight difference could just be felt between the two femora. Before this time the swelling of the lower end of the right radius had also considerably subsided, so that in fact there was no difference between the two wrists. The compresses were omitted at the end of a fortnight from the date when he was first seen, and he began then to make efforts to raise himself and to move his limbs about. A little gentle shampooing of the lower limbs and back with oil, and likewise douches of first tepid and then cold sea water were commenced at the end of a month. No physic was given to him except at first a single, then two teaspoonfuls of cod-liver oil daily, and an occasional powder of rhubarb and soda. Within eight weeks from the date when first seen, the boy, whenever allowed, would get upon his knees and could stand with a little support; he was of a ruddy colour, and his skin and muscles had become quite firm. He was still not allowed to bear the weight of his body on account of the slight knock-knee on the right side, but he was carried out every day.

(2) Analysis of principal symptoms.

The material from which this analysis is made consists of thirty-one cases. Of these nineteen have been already published. The majority of these cases have been recorded in German medical literature under the title of 'Acute Rickets' (Möller, Bohn, Forster, Hirschsprung, Senator, Petrone, Fürst). Some account of the disease is also given by Steiner and Baginsky in their respective treatises. Individual cases are referred to by these authors, but the accounts of them are too brief to admit of incorporation in the accompanying table*. Stiebel's description of acute rickets, which differs somewhat from the clinical picture given in common by the other authors, is also not available for this analysis, because of the absence of cases reported in detail. One case, briefly recorded under the title of infantile scurvy, by Dr. Ingerslev, also belongs to our group, and is, indeed, quoted by Hirschsprung a propos of his own case.

Sir William Jenner in his lectures refers to the occasional abrupt or acute onset of rickets, but does not specifically describe any case like those in question. The first English case on record is in the 'Pathological Transactions' for 1876. It was under the care of Mr. Thomas Smith at the Hospital for Sick Children, and is described under the provisional title of haemorrhagic periostitis.

Dr. Gee, in the 'St. Bartholomew's Hospital Reports' for 1881, has given brief notes of five cases, which he classes under the head of *osteal or periosteal cachexia*, pointing out the existence of an obscure bone lesion and of a marasmic condition not explicable by rickets or congenital syphilis. It will be found that these cases come within the group now under consideration.

In the 'Lancet' for November, 1878, and again in July, 1882, Dr. W. B. Cheadle has described two cases of the same kind which came under his care, and has referred to others. Dr. Cheadle has given reasons absolutely conclusive, as far as his own examples are concerned (in which spongy gums

* This table has been omitted in this reproduction.

were a marked feature), for the doctrine that the disease in question is a combination of rickets and scurvy; and his papers are in every way the most important contribution to the clinical side of the subject.

A French writer (Montfalcon) in the article on ' Rickets ' in the ' Dict. des Sciences Médicales ' (1820), gives a short paragraph on the complication of scurvy with rickets. He narrates a case of a girl, aged ten years, who was certainly the subject of scurvy of the gums and skin ecchymoses, and who had some obscure joint (?) or bone (?) affections. It seems extremely probable that the latter were scorbutic also, and the case is of some value in support of the view subsequently maintained in the following paper, that the essential features of acute rickets are truly scorbutic; but it is to be noted that the writer of the article in question gives no reason for the view that his patient was the subject of rickets, and, indeed, throughout his article uses the term rickets in an extremely vague and indeterminate sense. Further, this patient was much older than those (chiefly infants) the reports of which have already been referred to, and for this reason is not suitable for the analysis.

Eleven cases have come under my own care, and one has been communicated to me by Mr. Shoppee, and these with the nineteen before published constitute the material from which the analysis is made.

The invasion of the disease may be gradual or abrupt. After a few days inexplicable fretfulness, or several weeks' manifestations of pain, without obvious cause, when the limbs are touched, the child is rather suddenly taken off its legs, with more or less swelling of the lower limbs. In twenty-two cases out of thirty-one the thighs have been attacked, and in the same number (many of them of course the same cases) the legs. In two other cases the lower limbs are spoken of as affected without definite description. In a typical case both lower limbs, though to an unequal degree, are swollen tense, and shining, the skin is generally pale, but may be reddish in colour, not generally hotter to the feel than the rest of the body, sometimes indeed colder. There is a varying amount of oedema, often more over the thigh than the leg or the foot. The tenderness on pressure is extreme; the child cries not only on movement but even on the approach of the nurse. In a severe case there is often continuous moaning as though the child were in constant pain. The child lies sometimes with one or both limbs flexed, but in the more severe cases with the limbs extended, or extended and everted in an immobile conditon, which has been called pseudo-paralysis. In less severe cases, even at the outset, and in more severe cases after the partial subsidence of the subcutaneous swelling, it is not difficult to appreciate that there is a cylindrical swelling which envelops the shaft of the femur to a varying degree. The longitudinal extent of this swelling may vary, it may be very slight and be confined to the neighbourhood of the junction region between the shaft and epiphysis, or it may surround the whole shaft. In the most severe cases of all, of which I have seen two examples, soft crepitus was to be obtained just below the hip-joint. This no doubt is a late and very severe phenomenon, but from considerations afterwards to be referred to, I think it probable that it may occur not

unfrequently, and owing to the excessive tenderness of the patient, which interferes with careful examination, may escape detection. In Dr. Fürst's case, after the conclusion of the illness, a sharp angular bending with some thickening was found in both femora though the exact site is not indicated. Nevertheless, the ordinary sequence of events with respect to the thigh is, first swelling of the whole of that part of the limb, then subsidence of the affection of the soft part, allowing the thickening around the bone to be appreciable, then very gradual subsidence of the bone thickening, leaving the limb without deformity. In one of Möller's cases and in Förster's case after the illness a marked increase of the length and growth of the limbs was noticed. This is, however, by no means a constant occurrence.

The affection of the legs was occasionally present without involvement of thighs, but whether it existed alone or in combination with the thigh affection, it was in all the cases in my experience less severe than the thigh affection. Here, also, it may be said, in general terms, that the thickening radiates from the junction areas of shaft and epiphysis. The fibula is always much less affected than the tibia. In one of Möller's cases there was still a little thickening of the bones of the legs when the child died of atrophy, and in Hirschsprung's case there remained at the end of the illness a little 'thickening of one ankle.' With respect to the upper extremity in two of the cases already referred to, there was soft crepitus obtainable below the knee. Probably also in another case there had been some separation in this junction region, for at the end of the illness the shaft of the tibia was found displaced backwards to a slight extent just below the upper epiphysis. With regard to the leg as with regard to the thigh, the rule is for ultimate resolution to take place without deformity.

Other bones may become affected either simultaneously or more commonly by subsequent involvement. In one of Dr. Gee's cases there was some swelling over both scapulae. The same condition was observed in one of mine, the swelling being much more marked in the right than the left, and affecting especially the infraspinous fossa.

The humerus was affected in nine cases, and the radius and ulna, either separately or conjointly, in twelve. In one case, there was soft crepitus obtainable near the upper end of the humerus on both sides.

In general, it may be stated, with respect to the upper limbs, that the swelling of the soft parts was much less and the thickening along the shafts much more limited in extent. In the majority of cases, indeed, the swelling was limited to the epiphysial region; and it may reasonably be asked how was this to be distinguished clinically from ordinary rickety enlargement of the wrist for example? To this it may be replied, as in the type case, that probably some of the swelling is truly rickety but that there is something over and above the rickety swelling. (1) The appearance of the two wrists is often unlike; the enlargement above one epiphysis, being greater considerably than above the corresponding one on the opposite side; (2) the extreme tenderness is not present in simple rickets; (3) the pseudo-paralysis which often obtains in these cases does not occur in simple rickets; (4) the marked

subsidence in a short time as in the type case is quite unlike the slow retrogression of an ordinary rickety enlargement.

With regard to the cranium, morbid conditions were found either during life or post mortem in eight cases out of thirty-one. The exact amount which belonged to the illness in question is difficult in all cases to assign. Setting aside for the present the marked cranial bosses (Parrot's swellings) which were found, and also the slight thickening near the sutures, it seems probable that some slight swellings on the parietals, which were found post mortem to be due to sub-periosteal haemorrhage, belonged strictly to the illness in question.

Further, there appeared during the illness some swelling of both upper and lower jaws, and some thickening of the zygomatic regions occurred, and likewise considerable tenderness of the occiput followed by some thickening.

Let us consider now the other structures involved in movement. With respect to the joints generally of the upper and lower limbs, although the phrase ' painful joint affection ' is more than once employed, there is nothing in any of the reported cases to lead us to believe that there was effusion into the synovial cavities. Senator, Fürst, and others, are most careful in their descriptions to exclude joint effusion. There was certainly no evidence of it in any of my cases.

The muscles generally in the severe cases were more or less wasted. It is difficult to estimate how much of this was due to antecedent rickets, but it is to be observed that several of the children had been in good condition before the illness began. In several the weakness of the back was most remarkable. No lesion of the bones was detected, but the prostration was often quite absolute. In Hirschsprung's case for a time there was great tenderness over the neck.

With respect to the skin and subcutaneous tissue, the anaemia in the severe cases was profound; besides the pallor there was noted sometimes a peculiar sallow, muddy tint in the complexion.

In one of Möller's cases sugillations appeared on one leg, and Hirschsprung says of his that ' in several places the skin was tinged bluish red.'

In one of Dr. Gee's there was an appearance over the sternum like that produced by a ' bruise.'

In one of Dr. Cheadle's there were unhealthy sores on the wrist and finger, and it was stated that a blow on the thigh had left ' a swelling for a considerable time."

In one of my cases extensive purpura appeared before the bone condition became manifest.

In one of Dr. Gee's and in one of my cases there was ecchymosis into the eyelids, and in the latter case also there was for a few days slight proptosis of one eye. Some conjunctival haemorrhage occurred in Mr. Shoppee's case.

The tenseness of the lower limbs is in the very severe cases very considerable, but it is remarkable how completely as a rule the swelling passes away. In one of my cases there was for a week or more a small, soft, fluctuating area just above the junction of the lower epiphysis of the femur with the shaft on the outer side of the thigh. This also underwent spontaneous absorption. In another case, which I believed to belong to the group, the affection was confined to one thigh. There appeared considerable swelling, which at one place on the outer side of the middle of the thigh gave at length some fluctuation. This was opened by my colleague Mr. Morgan, a little pus escaped, and the small diffuse abscess cavity very rapidly healed, leaving, however, considerable deep-seated thickening and (which could be appreciated after a time) marked thickening around the shaft of the femur. As this case is so exceptional in regard to suppuration, I have thought it wiser not to incorporate it with the others, the more so that as the other limbs were not involved there was no opportunity of comparing their progress to both typical cases, and so render its identity certain. It deserves further investigation whether the subcutaneous swelling may not occasionally in severe cases of the so-called acute rickets undergo a partial suppuration.

In almost every case very severe head sweating is referred to, but in several this symptom had existed from a very early period, and it may be questioned whether it was special to the illness under consideration, although a very striking feature.

Here may be conveniently considered the subject of the body temperature in these cases, and some details must be given because in the reports there is some divergence of results. Senator in discussing acute rickets insists that pyrexia is a constant accompaniment, but this is certainly too sweeping a statement.

The case which best supports this view is that of Dr. Fürst. Observations made every three or four days during a month, recorded some pyrexia lasting through that period. At the onset of the illness the evening temperature was 102·7°, and this was the highest recorded. Within the next five days 101·8° and 101·5° were registered, the first an evening the second a morning temperature. After this no temperature higher than 100·4° was recorded, and at the end of the month it was 99·8°. It is important to bear in mind that in Dr. Fürst's case during the first eleven days, there was progressive involvement of different limbs, viz. first the left thigh and leg and right leg, then the right forearm, then the right arm, then the left arm and forearm, and that even so late as the twenty-fourth day there was some infiltration and tension about the left arm. After the end of a month no further observations were taken as the child was improving. Six weeks after this a relapse occurred which affected both zygomatic regions and the right thigh—this thigh not having been previously attacked. The temperature rose to 102°, but in a fortnight had become normal again.

Petrone gives the temperature of his case at the outset as 102·9°, but does not mention what it was subsequently. Hirschsprung states that in his case the illness commenced with febrile symptoms, and that there

was marked but irregular pyrexia. In his case also there was successive involvement of left shin and foot, then of left forearm and head of humerus, then of right foot, then of upper, then of lower jaw, which afterwards relapsed.

In Thomas Smith's case the temperature was observed twice daily during the six days that the child was in hospital. The highest temperature was 101·4°. On another occasion it was 101·2° and at other times it ranged between 97·4° and 100·6°.

This case was very severe in regard to bone lesions, but I do not think there was proof of any fresh start of bone-mischief during the week that she was in hospital. Furthermore, the child was suffering from some bronchial catarrh, and post mortem a small patch of consolidation was found.

In the type case I have mentioned that the rectal temperature when I first saw the child was 101°. This was probably the twenty-sixth day of his illness. An intelligent nurse told me that there had been some fever for several days.

Three days later the rectal temperature was 99·4°, and subsequently taken every day was scarcely ever above 99° There was no reason to suppose that any fresh bone-mischief supervened after the twenty-sixth day. In one of my cases, twenty-two days after the onset, the axillary temperature was 99·8°, and in another, ten days after the onset, rectal temperature was 99·6°. In several others, although the temperature was not taken, it was noted that the skin was cool. Bohn states that in his case there was no fever, but the child was only brought to him one month after the onset.

In some of Möller's cases there was for a time a little local heat, but he states that there was no fever. In another case the temperature was not elevated at the onset, but at a later period the child was febrile, with some catarrhal conditions. In Dr. Cheadle's second case the temperature when first seen was 98°, and 99° is the highest degree recorded. In Dr. Cheadle's first case, during the six weeks that the child was in hospital the axillary temperature was either normal or subnormal, except on the day after admission, when it was 99·5°. When I saw this child in the out-patient room before his admission into the ward, his rectal temperature was 103°. So far as the history could be relied on this was between two and three months after the onset of the illness. In both these cases of Dr. Cheadle's it is important to note that no new manifestations of bone affection appeared after they came under care, and a definite line of treatment was promptly adopted by him.

To sum up these somewhat divergent results, it is clear that Senator's statement that pyrexia is a constant accompaniment of the disease cannot be accepted. It is not considerable in amount, nor does it show any special hectic character, and for long periods it may be absent. A careful examination will, I think, leave little doubt that, setting aside some cases of intercurrent catarrhs, the pyrexia, when present, is related to the bone affection, and that, not so much in regard to extent as to the amount of

tension present. Probably, with a fresh involvement of bone, if much stretching of periosteum occurs, there is a little fever, at all events for a short time.

Of the affections of the mucous membranes the most important is that of the gums. In fifteen out of the thirty-one cases there was some morbid condition present. In at least four of these there was sponginess with a tendency to bleed, and some putrid odour. Nine showed varying degrees of mouth affection, from slight swelling confined to the neighbourhood of newly-cut teeth up to general swelling of both gums, and in one case of the lower lip also.

As to the date of appearance of the stomatitis in relation to the swelling of the limbs, in some cases it was antecedent to the limb affection in others it occurred after the limb affection was well established, and in others it was probably simultaneous.

In one of Dr. Gee's cases, and in one of mine, the gums were not swollen, but there were small localized ecchymoses beneath the gum in the situations of the on-coming teeth.

It is very important to note that in six cases it is specially stated that there was no stomatitis. It is almost absolutely certain that in a great many of the other cases stomatitis, or, at least, sponginess, was conspicuously absent; for the reports are given by authors who were fully acquainted with the occasional occurrence of this symptom in this group of cases (Senator, Möller, and others), and it is reasonable to believe that the frequent absence of sponginess of gums is the cause of the scorbutic hypothesis often being dismissed, or not entertained, or regarded as unimportant.

The details with respect to disturbances of the digestive tract are not very complete. In two cases the bone affection appeared to start after a severe attack of diarrhoea. On the other hand, in a great many of the cases the intestinal condition was considered healthy at the time of onset of the acute symptoms, and there was no notable disturbance throughout.

In the ninth week of the illness in one of Möller's cases, severe diarrhoea with some bronchial catarrh occurred. In Hirschsprung's case there was for a time obstinate vomiting. This is very exceptional. In the majority of cases the appetite was maintained. In two of my cases children of four years and two years respectively, there was present the greatest antipathy to meat and vegetables, and one of Dr. Cheadle's patients, a boy aged thirteen months, had very great dislike to gravy and potatoes. But in these cases this dislike was long antecedent to the illness in question.

There is very little noted with respect to the liver. Slight enlargement of the spleen and lymphatic glands occurred in Petrone's case. The former I believe, is exceptional, for in several other cases, absence of enlargement of this viscus is specially noted. In one only of my cases was the spleen palpably enlarged in a child in whom there was some suspicion

of congenital syphilis. The spleen continued larger than normal after the bone affection had subsided, and possibly had existed previously.

The accounts of the urine are somewhat scanty. In one of Dr. Gee's cases there was haematuria for a short time, and this was also noted in Mr. Shoppee's case. In Dr. Cheadle's two cases there was for a few days a definite trace of albumin. In one of Möller's cases and in Mr. Shoppee's, for a time there was a considerable deposit of uric acid. Both Bohn and Hirschsprung specially note that in their respective cases the urine was normal, being free from albumin or excess of phosphates, and this also was the case in the type case given at the outset of this paper.

There is nothing important to note regarding the heart and lungs.

With respect to the nervous system, extreme fretfulness must be mentioned as a symptom so striking and constant that everybody who has recorded cases has dwelt upon it as something quite remarkable in this affection. In fact this is one of the five constituents, viz. pallor, wasting, immobility, swelling of limbs, and fretfulness, which, with or without swelling of gums, pretty nearly sum up the clinical whole of the so-called acute rickets. This special fretfulness is amost certainly related to the affection of the limbs.

The laryngismus stridulus and fits which occurred during the illness in Dr. Fürst's case, and the tetany and laryngismus which occurred a short time before the onset of the bone symptoms in one of mine, belonged doubtless to the severe rickety diathesis which both these children presented. No manifestation of this kind occurred in the case of children who had been previously healthy.

There remains to be considered, in this section, the duration of the disease.

Slight differences of reckoning depend on whether the end of the illness is considered to correspond with the entire or partial disappearance of bone thickening, the child being well in other respects. Excluding the comparatively mild cases, there are the rather wide limits for the duration of one month and six months. The duration in the greatest number of cases is between two, and three and a half months.

It will be seen from the table that the disease is a very fatal one; no less than seven out of thirty-one died. It is equally remarkable to note the slow but gradual, and apparently spontaneous, tendency to complete recovery which occurred in others, even when the cachexia had been very profound.

Two of the cases, viz. Bohn's and Mr. Thos. Smith's, appeared, from the history, to have passed through similar attacks many months previously.

(3) Post-mortem appearances.

Although the German physicians have given such careful accounts of the symptomatology of this disease under the designation of acute rickets, they have no description of the morbid anatomy to offer, and this accounts for their very vague and unsatisfactory explanation of its pathology.

Professor Möller in his second paper describes two cases. One of these is fairly typical. The other was a marasmic child aged fifteen months, who was brought with exophthalmos and sanious discharge from the nostrils, and who died from exhaustion. On post-mortem examination an extensive haematoma was found under the frontal and anterior parts of the parietals, extending down to the orbital plates of the frontal and to the ethmoid and into the orbits. The blood was believed to be derived from the inner surface of the bones of the skull in which no thickening was found, but the vascular canals of the inner surface of the frontal were considered to be wide and the bone itself somewhat porous. No affection of the limb bones either during life or post-mortem was found. The case can therefore in no sense be regarded as agreeing with the typical examples of so-called acute rickets, of which the foregoing analysis has been given, albeit I am not prepared to say that it has no alliance with them.

It must in justice be stated that Förster made the shrewd guess with regard to the affection of the limbs in typical cases, that the essential condition was a sub-periosteal haemorrhage; and Möller, in some parts of his paper, seems to have come very near to that view, but in his summing up he speaks in a vague way of ' acute rickets as being solely a developmental disease in which there is a precipitate and tumultuous bone growth, which at times destroys the organism, killing through exhaustion, but most often is overcome leaving behind it a marked increase in the length of the limbs.'

A much simpler doctrine will I believe be elicited from the study of the clinical phenomena in the light of post-mortem examination.

I have made three autopsies on cases of the disease under consideration. The first was on a child under the care of Mr. Thos. Smith at the Hospital for Sick Children in February, 1875. Mr. Smith has recorded the case in the ' Pathological Transactions,' Vol. xxvii, p. 219, under the title of ' Haemorrhagic Periostitis of the Shafts of several of the Long Bones with Separation of the Epiphyses.'

Although many of the points in the clinical history of this and the two following fatal cases have been embodied in the foregoing part of the paper, yet in order to show the correspondence of certain morbid appearances with the clinical picture of the disease it is necessary that details of the history should be given with each fatal case, even at the expense of repetition.

Mr. Smith's case was a female child aged 1 year 11 months. She had been suckled for three months and subsequently fed on cow's milk and corn flour. There was no reason to think from the history that she had had congenital syphilis; but her rickets had been shown in her not cutting a tooth till she was twelve months old.

When thirteen months old, in April, 1874, her feet, legs, and thighs gradually became swollen and excessively tender, and, according to the mother's statement, ' hung down cold and dead.' This continued so for two months, and then there was slow improvement, so that by summer the swelling and tenderness had gone and the child was considered well, but for diarrhoea to which she had been subject more or less since six months old.

At Christmas, 1874, the child being then twenty months old, the swelling appeared again in both lower limbs, first in the feet and legs then in the thighs. After a month the swelling of the feet had considerably diminished but that of the thighs had increased. She had sweated a great deal. The bowels were only opened twice or thrice daily and the motions were not offensive.

When admitted on February 26, 1875, that is, two months after the beginning of this second illness, she was an extremely pale and cachectic child. She was rickety with a large fontanelle and beaded ribs. She lay on her back with her lower limbs flaccid, never raising them. There was some oedema, more in the thighs than the legs, and scarcely any in the feet. The skin was natural in colour and not hot to the touch. There was some prominence in the region of the trochanters, the thighs projecting outwards there, more on the right than on the left side. On lifting up the limbs distinct softish crepitus was obtained without the slightest difficulty just below the hip-joint and knee-joint on either side. It was evidently produced below the epiphyses. The hip-joints and knee-joints seemed natural. There was no oedema elsewhere.

I regret not to have recorded a note at the time about the upper limbs. But a note taken a few days afterwards in the post-mortem room about them may be here intercalated, to the effect that there was crepitus obtainable below the head of each humerus but none in connection with the elbows or wrists. None of the epiphyses could be considered very large.

The child coughed a little and there was abundant sharp râle over both backs with some doubtful resonance at the bases. There was nothing abnormal to be detected in the heart or abdominal cavity. The urine could not be saved.

During the week she was in hospital the child lay on her back and whimpered a great deal, and continued extremely marasmic. She died rather suddenly, the cause being not perfectly obvious, but she was very feeble, and had, moreover, a considerable amount of bronchitis. Her temperature in the axilla had been as follows:—

February 26.—Evening 101·6°.
27.—M. 100·6°. E. 100·6°.
28.—M. 98°. E. 100°.
March 1.—M. 97·4°. E. 101·2°.
2.—M. 99·6°. E. 98·4°.
3.—M. 100°. E. 98°.
4.—M. 99°.

At the post-mortem examination the lower limbs were first examined.

On the left side the glutaeus maximus was found rather pale, but nothing else was noticed abnormal about it, or about the muscles attached round the head of the femur.

The vastus externus was swollen, pale, and pulpy. A little yellow serum bulged out of the upper part, and on cutting into the muscle some blood was found extravasated into its substance, and the same character applied to the

vastus internus and crureus. The blood was pretty uniformily diffused through the deeper layers, and no coarse laceration was seen.

On making an incision down to the shaft of the femur, the periosteum was found separated from the shaft entirely in a continuous sheet. It was about $\frac{1}{8}$th inch thick, and was intensely injected all over the inner surface.

The shaft of the femur was separated from the epiphyses, and was almost entirely surrounded by a layer of maroon coloured blood clot, $\frac{1}{4}$ to $\frac{1}{2}$ inch thick, which loosely adhered to it, and in fact separated the shaft completely from the periosteum. On removing a little of this clot, the surface of the shaft of the femur was seen to be perfectly smooth. The ends of the shaft were not splintered, but had a ' sugary ' surface. There was no lymph or suppuration anywhere.

The abruptness with which the changes were confined to the shaft was very striking.

The hip-joint was natural, and so were the lower epiphysis and knee-joint.

There was no extravasation of blood in the muscles of the leg.

The changes round the tibia were not so extensive as round the femur, but they were of the same character. The periosteum was thickened, vascular, and separated from the upper and lower thirds of the shaft by a thin layer of blood.

In the middle third there was no blood; the periosteum was adherent to the bone, but easily stripped up. The shaft did not, as the femur, lie absolutely separated from the epiphyses, but it was loosened at the upper end.

The left fibula at its upper extremity was natural: there was, however, separation of periosteum and effusion of blood to a slight extent at the junction of the lower epiphysis with the shaft. The ankle-joint was natural.

The right femur presented almost identical appearances with the left. There was a minute spot of blood in the floor of the acetabulum, but nothing else abnormal in the hip-joint.

The right tibia and fibula also presented almost identical characters with the corresponding bones of the left side.

The upper limbs were not examined beyond the ascertaining of the crepitus below the head of each humerus.

The abdominal organs were natural, and so was the heart.

There was some collapse in both lungs, and in part of the lower lobe of the left a small wedge-shaped patch of consolidation, very like a past pulmonary apoplexy, over which was a little velvety lymph.

As in this case, I regret to say I was responsible for the suggestion of the term haemorrhagic periostitis, there can be no impropriety in my now criticizing it.

It was a provisional term employed to designate what seemed a remarkable and exceptional condition, but it would no doubt have been better to have described it as simply sub-periosteal haemorrhage.

For there was, indeed, as is fully stated in the report, no proof of any true inflammatory process, and the appearances were, to a great extent,

explainable by a primary haemorrhage from the periosteum, the cause of that haemorrhage, whether from damaged nutrition of capillaries, altered blood state, or both, being still an open question.

The second post mortem was made on a female child, L. S., aet. ten months, who was brought to me as an out-patient in October, 1881.

She had never had breast milk, but had been fed first on condensed milk, then on cow's milk, and then on various foods; at the time when she was brought to the hospital she was taking Anglo-Swiss food. A teaspoonful of cod-liver oil had also been given to her thrice daily for two months. Careful inquiry failed to elicit anything in favour of syphilis, and subsequent examination of the other children was negative in this respect, although they were found extremely rickety. The mother was a delicate woman, but the father was healthy. The house seemed to be wholesome. This child had had much head sweating since she was three months old. Bowels had been constipated until two months ago, when she had a severe attack of diarrhoea, and after this her legs were noticed to be very tender. Three weeks ago her wrists also became very tender. When brought to the hospital she was extremely fretful. She not only screamed directly she was approached, and still more when she was examined, but continually whimpered as though in constant pain. Her axillary temperature was 99·8°. Her skin generally was pale to the last degree. There was ecchymoses in both upper eyelids; also underneath the mucous membrane of the gums in the lower median incisor regions, and also in the lower molar regions separate ecchymoses were present. The child had not cut any teeth. The lower end of each radius was much enlarged, and the left hand hung prone in a condition of pseudo-paralysis. The left thigh was strongly flexed. There was some deep thickening to be felt along the lower third of the shaft of the left femur. The epiphyses of the lower limbs were a little enlarged. She lay on her back and never attempted to move. She was so ill that a complete examination could not be made, but it was ascertained that the liver and spleen were not enlarged. It was not expected that she would live, but the mother was ordered to give her as much raw meat juice as possible, and to continue the cod-liver oil. In a week's time she was brought again, and her condition was not worse, with the exception that there was slight proptosis of the left eyeball, as though there might have been some extravasation into the areolar tissue of the orbit. Eleven days afterwards this had subsided, but the child was paler and feebler, and she died October 29, i.e. three weeks after she had been first seen, the total duration of her illness being about three months.

The post-mortem was made with considerable restrictions. Body wasted.

Cranium.—On the external surface of each parietal, just behind the fontanelle, there was found an area of thin sub-periosteal haemorrhage, about the size of a shilling. The bone underneath it was slightly porous.

Thorax.—The intercostal muscles and some of the other muscles on the thoracic wall, especially the left serratus magnus, of a pale yellowish colour and slightly pulpy consistence as through infiltrated with serum. The periosteum of the ribs extensively detached, thickened, rather vascular, and

slightly granular on the surface towards the rib, from which it was separated by a considerable quantity of flaky, chocolate coloured débris. There was no lymph or pus, and the flaky débris was more like disintegrated blood-clot than anything else. The ribs were extensively bare and white and slightly rough. They were distinctly wasted. What had been taken for 'beads' of the ribs were simply the extremities of the costal cartilages. The bony part of the ribs was much wasted especially along the anterior surface. Thus the anterior extremity of the rib was by no means in complete apposition with the whole of the extremity of the costal cartilage. There was no beading on the inner surface. The ribs were extremely brittle. They contained only thin soft medulla, and when this had escaped the rib was a mere shell. It was a wonder that the ribs had not separated at their junctions with the costal cartilages, or that some of them were not fractured beyond. They could be snapped in two easily. On the parietal pleura of both sides there were numerous petechiae along lines corresponding with the ribs. There was a quantity of blood-stained serum in the left pleura but no lymph. In the middle of the left lung there were two or three very small masses of caseous tubercle and a few gray granulations on the surface in this neighbourhood. There was no disease of the right lung or pleura, and the bronchial glands were healthy. There was no disease of the other viscera.

We were not allowed to examine the lower limbs completely, but some extravasation was found partly into the periosteum near the left crista ilii and the deeper part of the muscles attached there, whilst the superficial parts were pale and slightly pulpy. There was also some subperiosteal haemorrhage in the region of the junction of the upper epiphysis of the femur with its shaft.

The third post mortem was also made on a female child, D. L., who was an out-patient of my colleague's, Dr. David Lees, to whom I am indebted for ultimately transferring the case to me.

The child was not regarded as syphilitic by Dr. Lees or myself, but the following points of family history ought to be stated. The first child had been born dead at seven months. The second died aged four months, cause unknown; the third was a full-time healthy child; the fourth was full time and suffered much from spasmodic croup and fits.

The mother stated that she was in good health during pregnancy with the child now in question, who was the fifth. The child was full time, is said to have snuffled occasionally but had no rash. She was suckled exclusively for seven months and not finally weaned till eleven months old. From seven months old, in addition to her mother's milk, she had cow's milk and two teaspoonfuls of Chapman's entire wheaten flour in the milk thrice daily; she never had condensed milk. At the time when the limbs became bad, i.e. at seventeen months old, the mother states that she was giving her the best part of a breakfast-cupful of beef tea fresh-made every day with bread and farinaceous puddings and a little milk, not more than half a pint. No vegetables whatever were given to her. The mother affirms that the child had six teeth at six months. She was, however a weakly child from four

months onwards. At nine months old she began to suffer from laryngismus, and she was first brought to the hospital on this account when fifteen months old. She was decidedly rickety, had frequent diarrhoea, and when about seventeen months old began to be very tender, especially about the lower limbs.

When she was admitted under my care, December 9, 1881, she had had this extreme tenderness for two months, gradually becoming worse, so that she could not be touched anywhere except above the upper limbs without screaming. She was anaemic and flabby but not wasted, she sweated about the head considerably. The fontanelle measured 2 inches by 1; there was marked beading of the ribs, and the epiphyses of the upper limbs, especially at the wrists, were decidedly enlarged. There was some swelling over each scapula evidently belonging to the bone. On the right side it formed a low rounded tumour over the infraspinous fossa. Both were extremely tender to touch; there was no alteration of the overlying skin. Both thighs were swollen evidently from affection of the bone. The child was too sensitive to be examined thoroughly, but soft crepitus was obtainable above and below both knees. The legs were also tender and swollen, less so than the thighs. The child was ordered beef-juice, mashed potatoes, and one orange daily. On the fourth day after admission she developed a clangy cough, and on the fifth a typical rash of measles, from the supervention of which disease she died on the sixth day.

At the post mortem, examination of the limbs gave the following result:—There was considerable effusion of thin pale yellow serum into the substance of the muscles of the thigh, rendering the superficial layers pulpy. In the deeper layers there was tolerably uniformly disseminated blood-clot. The periosteum was thickened and, except at the upper extremity, separated from the shaft of the bone. Surrounding the shaft, and in some places bridging over the space between it and the displaced periosteum, was a thick sheath of blood-clot. There was no fluid contents in the periosteal sac nor was there any lymph or caseous material.

Along a line about $\frac{1}{4}$ inch. above the junction line of shaft and lower epiphysis the shaft was separated. The separation had taken place through the loose imperfectly ossified material at the end of the shaft. The opposing surfaces were rough but not splintered. There was no callus. The ossifying centre of the lower epiphysis was a great deal of it diffluent. It was larger than natural, in fact, of the diffuse form which Mr. Sutton has recently pointed out as characterizing the ossifying centre of rickety epiphyses. There was no cushion of cartilaginous material, such as is present in the early stage of rickets between the epiphysis and the shaft, but this, I take it, had been replaced by the loose imperfectly ossified material through which the fracture had taken place.

The muscles below the knee also showed the result of extensive blood extravasation in the deeper layers. The periosteum of the right tibia was thickened and vascular; there was blood extravasation between it and the shaft for the whole length, but it was greater in amount at the extremities than in the middle. There was fracture through the loose, imperfectly

ossified, brittle material, about half an inch below the line of junction with the upper epiphysis. The ossifying centre of the upper epiphysis was diffuse, red, and very soft. There was no separation of the lower epiphysis from the shaft. The medulla of the shaft was very soft and red, and the trabecular structure of the shaft broke down very readily; there was no trace of suppuration or caseous material.

The periosteum of the right fibula was not actually detached from the shaft but it was very vascular, and there was slight extravasation between it and the bone, especially near the extremities.

The femur and tibia of the left side corresponded closely with those of the right side except that there was less extravasation.

The right scapula had a firm layer of blood-clot on both the ventral aspect and on the infraspinous fossa. That situated on the ventral aspect had led to the complete stripping of the periosteum, and the osteogenic power of the periosteum was shown by the formation of a thin lamina of osseous material over part of the subjacent blood-clot.

The clot on the infraspinous fossae was also nearly $\frac{1}{4}$ in. thick, but I failed to detect any earthy material in the stripped up periosteum.

The right humerus did not present any periosteal lesions similar to those described above. It showed many of the features of rickets passing from the first to the second stage.

It is true the typical proliferated cartilaginous zone was no longer obvious as such, but its place was represented by a buff-coloured layer of imperfectly ossified material, and below this there was some loose trabecular bone.

The medulla was very red and soft and the trabecular structure of the shaft loose and scanty. There was no deformity of the shaft.

The radius and ulna were free from extravasation, and presented on section rickety characters very like those of the humerus.

The lumbar vertebrae presented on section a marrow which was unduly red and soft and a trabecular structure which was very easily broken down. The ribs presented characteristic beads which were undergoing partial ossification.

The cranium did not present any bosses, but close to the medio-frontal suture and in front of the fontanelle was slight thickening, which was evidently old.

Some microscopic sections of the shaft of the femur, kindly made for me by Dr. Money, show the periosteum vascular and thickened, but I think without cellular infiltration; extensive haemorrhage in the deeper portions and also between the periosteum and the bone; considerable absorption of the trabecular structure with large spaces showing in places slightly eroded margins; at the upper extremity rickety ossification.

There is a little to state about the viscera. The lungs showed many patches of collapse and some commencing lobular pneumonia. The bronchial glands were a little enlarged. The liver and heart were healthy. The spleen weighed nine drachms and was firm to the feel. There were some small, flat extravasations of blood under the capsule, and also some patches with a

superficial area about the size of a shilling, of extravasation in the substance of the spleen, which, however, appeared to have caused but little laceration. The kidneys and intestines and peritoneum were natural.

We may now sum up the morbid appearances as far as these three cases are concerned, and add these to the general synopsis of symptoms.

Lower limbs.—Muscles: serum in the upper layer, which, probably partly as the result, are pale and slightly pulpy. Deeper layers contain extensively disseminated blood-clot.

Periosteum of femur and tibia thickened, vascular, separated from affected bones in great measure by sheath of blood-clot.

Fracture through loose trabecular structure at extremities (one or both) of shafts of femur and tibia. No callus. The two bony surfaces rough but not splintered.

I would suggest that the subperiosteal blood extravasation is the first event and the fracture the second. The extensive blood extravasation probably interferes with the nutrition of the bone, and thus the very minimum of violence, such as an ordinary movement, may lead to fracture.

The medulla of the shafts soft and red, and the trabecular structure scanty and friable.

Upper limbs.—Extensive blood extravasation under periosteum of both dorsal and ventral surfaces of scapula.

Unfortunately, with respect to the long bones, no complete post-mortem evidence is yet obtained, but there can be little doubt that in some of the cases that recovered there existed for a time a haemorrhagic extravasation in the neighbourhood of the junction of shafts with epiphyses, especially near the wrists.

Ribs.—Extensive separation of periosteum, probably by blood-clot. Ribs wasted, bare, and brittle, with very thin red medulla. Ribs very readily separable from junctions with costal cartilages.

Cranium.—In one case subperiosteal haemorrhages in position where Parrot's bosses are often found, and inasmuch as the scapula in one case showed new bone formed in the upraised periosteum, it seems possible that bone might also be formed over the subperiosteal haemorrhages on the cranium and give rise to a condition indistinguishable from a cranial boss.

Visceral changes.—Blood-stained serous pleural effusion and petechiae along the parietal pleurae in the second case; haemorrhage under the capsule and into the substance of the spleen in the third, and the small haemorrhagic focus in one lung in the first, though perhaps not of great importance, are interesting from their association with the subperiosteal haemorrhage.

(4) Etiology.

We must now ask what is the etiology of the disease under consideration, how is it to be distinguished from other diseases with which it has points of resemblance, and with what disease known to us has it the closest affinity.

Approximate answers to these questions will be best obtained by reviewing some of the conditions under which the symptoms arise.

As to age: My earliest case occurred in a child of five months, but Senator has described one in a child aged four months, and Steiner says the disease may occur as early as the fourth month. Of the thirty-one cases analyzed twenty-six belonged to the first two years of life, and five to the second two years of life. Of the twenty-six cases belonging to the first two years, half belonged to the first year and half to the second. Dividing into periods of six months, the greatest number of cases occurred between six months and eighteen months of age, so that as far as our numbers help us the disease would appear to be pre-eminently a disease of the second part of infancy.

The sex is not stated in all the reported cases, but from the data forthcoming there appears to have been twelve males and eleven females, so that sex cannot be considered of any importance.

With respect to period of the year in which the symptoms become manifest,—Hirschsprung asserts that the disease always occurs in the winter months. This is much too sweeping a statement. Out of twenty-eight of which accurate data are given, seventeen occurred in the colder six months and eleven in the warmer six months. Probably a greater preponderance would appear if we had the dates of all the cases.

Although most of the cases belonged to the poor, there were several quite typical amongst children of those who were well to do, and there is nothing of importance to be elicited about the dwellings of the patients, which in some instances at all events were perfectly satisfactory.

It will be convenient to discuss the important question of diet at a later period, but possible hereditary causes may now be considered.

In several the mother was delicate, and in some of the cases other children were rickety in the ordinary sense, but in others the parents were healthy and the other children healthy. It does not appear from any of the histories that any other member of the family in any given case had suffered from the symptoms of so-called acute rickets, at least there is no statement to the effect that more than one member of the family suffered in this way, which is sufficient if not conclusive.

In regard to hereditary syphilis it must be admitted that it is difficult to prove a negative because the so-called acute rickets rarely develops during the period when the early indubitable syphilitic signs are present.

Steiner states that of the ten cases seen by him acute rickets supervened on congenital syphilis in two children aged four months, and that these two children soon died. As no post-mortem account is given of these cases it is open to us to ask whether the disease from which they suffered may not have been the congenital syphilitic affection of the ends of the shafts of the long bones which has been described by Wegner, Parrot, and others.

For, truth to say, this disease has some clinical features not unlike those which I have described as belonging to the so-called acute rickets, and it is desirable here to refer to the similarities and differences between the two.

The junction area between the shaft and epiphyses is specially affected in both, and in the syphilitic affection there may be some accompanying

perichondritis and periostitis, which latter causes a swelling for a varying distance up the shaft. Also in the syphilitic disease there may be, as I have several times observed, displacements of epiphysis from shaft. Further, pseudo-paralysis, which is very common in the syphilitic disease, may occur especially about the wrists in the cases which occupy our attention. But in the syphilitic affection the pain and tenderness are not nearly so severe as in the disease under consideration; they are often, indeed, quite trifling in amount, whilst in the so-called acute rickets they are more continuous and more severe than any bone disease of childhood with which I am acquainted.

There is occasionally a concomitant joint-effusion which may be purulent in the syphilitic affection. I think it is doubtful whether the joints themselves are affected in acute rickets. In a typical case of acute rickets in which the thigh is affected, the involvement of soft parts is more extensive than is ever met with in the syphilitic affection of the end of the shaft.

Finally, the element of age is of very great value.

Acute rickets, as I have shown, is very rare in early infancy, whilst the typical congenital syphilitic affection is common under six months, indeed, under four months, and even occurs in the foetus. But it must be confessed the only thoroughly satisfactory distinction is one derived from post-mortem examination. In the syphilitic affection, of which I have examined three specimens post mortem, and of which specimens have been shown in this country by Mr. Haward and Dr. Goodhart, the change is mainly, as M. Parrot has pointed out, an endosteal one, and consists of what he calls a gelantiniform transformation of the ossiform material which exists as the extremity of the shaft. It is quite different in character from the massive proliferation of cartilaginous material found in an ordinary case of the first stage of rickets, which material forms a large cushion between the shaft and the epiphysis.

In the syphilitic affection, along the gelatinous softening, there may be a varying amount of concomitant perichondritis and periostitis, which latter, as I have said, may extend up the shaft for a varying amount and be followed by an osseous deposit. But I have not seen in the syphilitic affection the extensive separation of periosteum and shaft by a mass of blood-clot such as occurs in the specimens of so-called acute rickets now under consideration, and such a striking condition has not been described by Wegner or Parrot who have both examined a great many cases.

But the affection of the ends of the shafts is by no means the only form of syphilitic affection of the long bones. Cases may be seen in older children where several long bones are thickened along the greater part of the shaft with firm solid deposit. This condition may last for months and slowly clear up. How is this to be distinguished clinically from acute rickets? I can only say that I have never seen a syphilitic case of this character lying prostrate with the pain, tenderness, and cachexia comparable with that we have already considered, but that in fact the general suffering and the progress are quite different.

To return to the cases analyzed in this paper. In the greater number, as I have said, the early indubitable signs of congenital syphilis are no longer capable of being brought into evidence on account of the age of the children, but are there any other signs available which might help us in this direction? In no less than eight cases either the facial or cranial bones were affected, and in two if not three there were bosses on the frontals or parietals of the kind described by M. Parrot as characteristic of congenital syphilis. Now, although it is certainly the fact that many unquestionable syphilitic infants develop these bosses, especially if they be also rickety, yet in our present state of knowledge it seems to me premature to regard them as decisive of the question of congenital syphilis in the absence of other signs.

In one of my cases, along with these cranial bosses had marked splenic enlargement, and both these conditions persisted after the affection of the limbs and the sponginess of the gums had subsided, not under mercurial or iodide treatment, but under raw-meat juice and vegetables. In this case I have unfortunately lost the early history; the conclusion I had formed was that the child was possibly syphilitic, but that this had nothing to do with the condition of the limbs.

The early infantile history of one of the three cases of which post-mortem notes have been given, was compatible with congenital syphilis, but there was nothing conclusively syphilitic found post mortem.

It must be remembered that although the effects of syphilis may last for a considerable time, and seem to have a very special incidence upon and proneness to relapse in the osseous system, yet that they may also very rapidly pass away. Thus I made a post-mortem examination on a child aged ten months, who died of acute tuberculosis without any syphilitic lesion, and whom I had had under observation when it was an infant with severe congenital syphilis. There must be many parallel experiences.

To sum up these observations it may be stated—(1) that of the cases recorded in the great majority there was no conclusive proof that congenital syphilis was actively present; (2) that in several there was nothing in the previous history to justify the view that congenital syphilis had been present in early infancy; (3) that even in those in whom infantile syphilis had possibly existed it would not necessarily follow that the symptoms of acute rickets had any connection whatever with the infantile syphilis; (4) that it seems possible that two cases, briefly mentioned by Steiner, of children four months old, who were the subjects of congenital syphilis, and considered by him to be also suffering from acute rickets, were really the subjects of the special syphilitic affection of the ends of the shafts of the long bones which presents considerable resemblances to the so-called acute rickets.

We must now consider the relation of the disease in question to the ordinary form of rickets with which we are so familiar.

Was rickets present at all in the ordinary acceptation of the term? In nine cases the details are not sufficient to allow us to give a definite reply. Of the twenty-two remaining cases reference to the table will, I think, show

that in at least three the signs or ordinary rickets were very pronounced indeed, in seven moderately well marked, and in nine slight.

In at least three we are justified in saying that there was no rickets, and amongst the nineteen slight cases the evidence often amounts to nothing more than slight beading of ribs.

Hirschsprung asserts that the disease has always appeared in formerly healthy children. This is another of the sweeping statements of a very able observer. But, although the statement is not accurate, yet it is remarkable that many of the children before the sudden onset of the disease were considered to be in fair general nutrition.

In Dr. Fürst's case, after the subsidence of the acute symptoms, marked bendings of the femora were found which had not occurred before the illness. and which he considers established the truly rickety nature of the illness.

I believe that even that condition is susceptible of another explanation, but whether that be so or not let it be noted that in several of the recorded cases the recovery was absolute without deformity within a period of three or four months, which is quite unlike the ordinary course of rickets.

We are confronted then by two difficulties:—1st. The complex of symptoms which we have described may occur in a child in whom the ordinary signs of rickets are practically nil; and 2nd. very severe cases of rickets, in the ordinary sense, may run their course without presenting the complex of symptoms which we have descibed.

There is little wonder then that the German writers have found it difficult to 'dovetail' the so-called acute rickets with ordinary rickets, the more so that it is admitted that acute rickets so called is quite a different thing from severe or aggravated rickets.

I do not think that anybody will maintain that the subperiosteal haemorrhage in the cases of which the post mortems have been given (and which also I assume to have been present in the cases analyzed) is a feature of rickets as such.

I showed the specimens to Sir William Jenner, who told me that, in respect to the striking feature, viz. the subperiosteal haemorrhage, he had never seen it in ordinary rickets. There is also no description of such a condition in Guérin's account of rickets.

With respect to other diseases, I have already shown that, clinically and anatomically, the one in question differs from acute periostitis single or multiple.

The partial death of the shafts in severe cases is, I think, sufficiently explained by the mechanical interference with efficient vascular supply by the extravasated blood clot. In the cases which recover, the thickening of the bone shafts, which may remain for a considerable period may, I think, be explained by the osteogenic power of the upraised periosteum.

With what disease can we connect this non-inflammatory, sub-periosteal haemorrhage, associated with blood in the deeper muscular layers and serum in the superficial layers? Blood has been found in the joints in haemophilia, but it is not described as occurring under the periosteum in that disease.

In the group of cases analyzed there is, I think, no proof of effusion into the joints, although once or twice the term 'painful joint affection' is used. In a great many, at all events, there is no sign of effusion. But certainly the clinical history of our group is very different from that of one of the arthritic attacks of haemophilia.

It is a question how far purpura ought to be ranked as a separate disease, and whether it would not be desirable to consider it rather as a symptom occurring in many diseases. Although sugillations occurred a few times in our present group it is interesting to note that only in one case are small, numerous, spotty ecchymoses in the skin recorded. Without attempting to define purpura haemorrhagica, I may mention that in a few cases (to which for want of a better this term might have been applied) I have seen general painful swelling of the leg occur along with the appearance of purpuric spots in that region. This painful swelling has, however, so far as I have seen, only lasted a few days, and thus differs considerably from what obtains from our present group.

Although it would be absurd to limit the possible occurrence of sub-periosteal haemorrhage to any one malady, I believe it will be found, on analysis of the cases before us, that they approximate more closely to scurvy than to any other disease with which we are acquainted. Let us consider the parallelism first along anatomical lines.

The painful brawny induration of the lower limbs in adult scurvy was shown by Lind to be due to blood extravasation in the bellies of the muscles and serum in the tunica adiposa (p. 496, 3rd edit.) He often found the blood extravasation most extensive in the deeper layers, and laying on the periosteum; and once he discovered lying in spoonfuls beneath the periosteum.

Dr. Budd, in his article on 'Scurvy,' in Tweedie's 'System of Medicine,' describes a post-mortem on one case in which, although there was no swelling of the calf, there was a node-like swelling over one tibia, and on cutting down upon it there was found a thin layer of blood under the fascia and a solid clot of chocolate colour a line or two in thickness for a length of six or seven inches under the periosteum, the periosteum itself being thickened and infiltrated with blood in this region. Other sub-periosteal haemorrhages were found on one femur, one fibula, the opposite tibia, and the upper and lower jaws.

There are some older observations which are still more interesting. In the year 1699 M. Poupart made some dissections of scorbutic bodies in the Hospital of St. Lewis, at Paris. Amongst his remarks is the following, quoted by Lind:—'In some, when moved, he heard a small grating of the bones. Upon opening those bodies the epiphyses were found entirely separated from the bones, which by rubbing against each other occasioned this noise. All the young persons under eighteen had in some degree their epiphyses separated, and 'in some' he says 'we perceived a small low noise when they breathed,' and in them the cartilages of the sternum were found separated from the bony part of the ribs.

He further describes a condition of rib very like that to which I have referred in my second post mortem.

There is another observation by Dr. Godechen, a Russian physician, which is quoted by Budd, and is very important. In a case of scurvy, separation of the ribs from the costal cartilages and fractures of ribs near their anterior extremities occurred, without violence, whilst the patient was in the hospital.

Without laying too much stress upon it. I may refer to the blood-stained effusion in one pleura in my second post mortem as being comparable with the condition of the pleura found in some of the fatal cases of adult scurvy.

Having shown, then, a certain anatomical resemblance between our group of cases and adult scurvy, let us work back along the clinical lines and see how far they also run parallel.

The order of appearance of symptoms, as set down by Lind in his own words, is, first 'a change of colour of the face, from the natural and usual look, to a pale and bloated complexion with a listlessness to action.' The second symptom is a stiffness and feebleness of the knees upon using exercise, and the third is the swelling of the gums.

In our group of cases the change of colour of the face is most striking. In a typical case it is not simple pallor but pallor of a somewhat dirty sallow tint. The general prostration is quite as marked a symptom. With regard to the swelling of the limbs during life, though it is true it is not so brawny in our cases as in the adults yet there are many similiarities. The distribution is singularly parallel. As pointed out by Lind, there may be in the adult only a single swelling, but more commonly the swelling is bilateral or indeed multiple; and this obtains also with regard to our cases. In both alike the lower limbs are in the majority of cases affected and in the greatest severity.

There are parallels also in distribution, to which I have already referred in the occasional involvement of the ribs and of the upper and lower jaws.

With respect to the gums, we have, it would seem, at first a remarkable divergence between some of our cases and the typical adult scurvy.

In fifteen cases out of thirty-one it is noted that the gums were affected. In a few of these the swelling was obvious and characteristic, as in Dr. Cheadle's two cases, especially the first, from which there was much bleeding. Also in the case of Dr. Ingerslev the sponginess of gums was accompanied by a carrion-like odour, which was no doubt sufficiently suggestive to him of the true affinities of the malady. But in several others the swelling was very slight, and in fact only consisted in small localized ecchymoses in the sites to be occupied by the coming teeth. In six cases it is specifically stated that there was no stomatitis, and in ten it is not mentioned as being present.

The question of scurvy was indeed considered at the time of making the post mortem of Mr. Thomas Smith's case, and dismissed on account of the absence of any swelling of gums.

But even in adults I have, since making the above post mortem, learned that the absence of swelling of the gums does not negative scurvy. Dr. Ralfe has informed me that in crews suffering from scurvy there have been well accredited cases of men who have had all the other symptoms of profound cachexia, etc., but without the spongy gums; and this view is also expressed by Dr. Buzzard in his article on scurvy in 'Reynolds' System,' and in his definition he implies that sponginess of gums is not absolutely essential. I believe it has been observed that if a man who has lost all his teeth gets scurvy subsequently, sponginess of gums does not occur. Sir James Paget has told me that it is almost impossible to salivate a patient who has lost his teeth, and the difficulty of inducing sponginess of gums in young infants by the administration of mercury is well known. It is interesting to note in our own group that where no eruption of teeth had occurred no sponginess occurred; that the sponginess when present was chiefly in the neighbourhood of teeth that had been cut, and that the small submucous ecchymoses when present were above the sites of the oncoming teeth. I submit, then, that this divergence is not sufficient to disprove the identification of the so-called acute rickets with scurvy. The history of the study of disease has led us to discredit universal propositions in medicine and to doubt the existence of an absolutely pathognomonic sign, that is to say, of a sign which is present in every case of a given disease and never present in any other disease.

To those who will be willing to admit that the cases with limb affection and spongy gums were truly scorbutic, whilst denying the scorbutic character of the cases of limb affection without spongy gums, I can only reply that in every other symptom several of these cases were as nearly as possible identical.

With respect to pyrexia there is another seeming divergence. I have already pointed out the inaccuracy of Senator's statement that in these cases some fever is an invariable and characteristic symptom, and I have suggested that the fever, when present and not due to intercurrent ailments, may perhaps be proportionate to the tension of the haemorrhagic effusion under the tight periosteum. The bones have not been carefully examined in a sufficient number of cases in adult scurvy to admit of a dogmatic statement, but it seems probable that in them the periosteum is not so extensively involved as in these children's cases; that in fact the blood extravasation and serous exudation are more superficial and may give rise to less tension. On the other hand, although scurvy in adults is generally an apyrexial disease, it must be remembered that, in the words of Dr. Budd, occasionally we find the skin hot and the pulse attaining or even exceeding the rate of 120 in the minute. In these cases, Dr. Budd remarks, the swellings are exquisitely tender and the slightest movement of the limbs occasions great suffering.

Thus, even in this respect, I think we may establish a certain parallelism.

There are many other parallelisms to be drawn from a further analysis, but we must no longer defer the consideration of diet as an etiological factor

of these cases. The great difficulty in this part of the inquiry is the paucity of information in many of the reports as to the quantity and quality of the food which was being taken at the time of the onset of the acute symptoms.

First, with respect to breast milk. Several of these thirty-one children had previously been suckled for varying periods, but with the exception of a dubious statement by Möller about his third case, I think none of them are recorded as being at the breast at the period of onset of the acute symptoms. Steiner, however, in his brief account of the disease, though he speaks of its onset as being generally after weaning, uses the phrase that it may even appear during lactation. I venture to suggest that these exceptional cases coming on during lactation may have been not so-called acute rickets, but examples of the congenital syphilitic bone disease which may appear in infants at the breast, if the subjects of syphilis.

In the cases at present under review, then, we have to deal with children fed at the time and for a varying period previously by hand, and it is of the greatest importance to see if there was any other point in common with respect to the food.

First, it will be found that certainly five, probably six, and perhaps more, were taking cow's milk at the time of onset. On further investigation, we find that in one case the quantity was extremely small, in another not more than half a pint daily; in a third it was two pints in twenty-four hours, with an equal quantity of water, the child suffering the while from considerable diarrhoea. We have no information about the quantity in the other cases nor indeed of the quality, which is probably important.

It is clear that the use of beef tea was not adequate to prevent the appearance of the disease, for in three cases, perhaps four, this food was being given at the time of onset.

It is very important to ascertain whether the affection ever appears whilst a child is taking raw-meat juice. The only case bearing on it is Förster's, but it is not explicit enough.

A child of eleven to twelve months old had been breast-fed for three months, then had had cow's milk, Liebig's soup, flesh broth, eggs, scraped meat, etc., and had suffered from jaundice and diarrhoea. But it is unfortunately not clear from the account of the case what was the exact diet at the time of the onset. This is important, because for several months the child had been well nourished in spite of jaundice and diarrhoea; and Förster notes that the evidence of rickets was very slight.

Two of my cases had hysterical objections to meat and meat and vegetables respectively. One of them cried and even vomited when I had a plate of meat set before him. Also in two cases of scurvy in older children not included in this analysis I have observed the same curious dislike. One of these latter children absolutely screamed whenever any vegetables were placed on the table anywhere near to her, and refused any kind of food offered to her if the spoon had been previously used for vegetables.

I cannot find that it is stated in any of these cases that at the time of onset fresh vegetables formed a part of the diet.

The most important fact is that in at least seven there was absolutely no fresh food given. Thus Nestlé's food made with water, Ridge's food made with water, mealy foods, exclusively amylaceous food, and Anglo-Swiss food are examples.* In some of the cases the food and hygienic conditions are said to be satisfactory, but as the details are not given we cannot discuss them.

What light does the result of treatment throw upon the disease? Möller's cases convinced him that anti-phlogistic remedies were distinctly injurious, and in Dr. Fürst's case they seem not to have been followed by any benefit.

Great influence is attributed by Bohn and Hirschsprung to the return of spring and the possibility of getting the child out, and this is parallel to the experience with regard to adult scurvy.

With regard to antiscorbutics, they appear to have been given in some of the German cases without, in the opinion of the authors, leading to obvious benefit.

I venture to suggest that, before arriving at a definite conclusion, it is necessary to know the exact period of the disease at which they are given. When the marasmus is very profound indeed, it is, perhaps, too much to expect an immediate improvement, or, perhaps, any improvement at all. And, moreover, when there is much sub-periosteal haemorrhage, it must take a considerable period before absorption can possibly be completed, and the bone return to a normal state. But in Dr. Cheadle's two cases, and in seven of my own, the improvement was perfectly obvious and most striking in those which could be personally supervised, and in which treatment could be persevered in, in spite, as sometimes happened, of objections on the part of the child.

In Ingerslev's case, it is noted that no treatment, including anti-scorbutics, led to the slightest improvement until the spring came, and the child was able to eat garden cress. This is parallel with an interesting observation recorded by Dr. de Mertans in the 'Philosophical Transactions' for 1778. This physician, who was attached to the Foundling Hospital at St. Petersburg, had been accustomed to treat many severe cases of scurvy in children, especially in the winter and spring, and a very fatal disease he sometimes found it. Experience taught him that if the cases came under his care early in the disease vegetable soups succeeded very well, so that three or four weeks were generally sufficient for cure. But in one winter the outbreak was particularly severe and resisted his ordinary treatment, and he then found that the most stubborn cases yielded only when he gave them raw vegetables as well as vegetable soups ('Phil. Trans.,' vol. lxviii, p. 676).

* To which I may add, from two subsequent cases not included in this analysis, Savory and Moore's Food and Neave's Food.

Reverting to our cases it is clear that they differ very much in severity. Those in which the cachexia is very profound often end fatally, just as in adult scurvy. Nevertheless, a careful perusal, especially of the German cases, convinces me that the disease in question often tends towards a slow, but ultimately complete, recovery, and this independent of any special treatment.

Let us turn once more for a parallel in adult scurvy to Lind, whose work is such a masterpiece, not only of learning, but of accurate and candid observation. Lind's arguments for the employment of fresh vegetables in scurvy are unanswerable, but it is interesting to read in the postscript to his third edition, concerning certain cases that he had carefully watched, that 'strict abstinence from the fruits of the earth was continued long enough to convince me that the disease would often, from various circumstances, take a favourable turn, which cannot be ascribed to any diet, medicine, or regimen whatever.'

It may very properly be asked why, if it be true that these cases are mainly produced by a faulty diet, are they not more frequently seen, since a faulty dietary must obtain in London and other large towns to an extreme degree, especially amongst the poor?

A complete answer to this question cannot be given. But first, probably minor, degrees of scurvy are not so rare as might be thought.

It is possible that some slight cases, and even severe cases of the bone affection, are dismissed as ordinary rickets, with an excess of tenderness and fretfulness. Probably, also, in this affection as in others, idiosyncrasy plays a part; and we have to remember that in adults the scurvy-producing diet may be in use for a considerable time before the disease is precipitated, so to speak, by some additional, often unknown, depressant agency.

A valuable remark of Dr. Cheadle's may, however, be referred to in regard to the reason why scurvy does not more often occur amongst the children of the London poor. A bread and butter diet, with the exclusion, or extremely meagre supply, of milk is common enough, and is probably responsible for a great deal of rickets, but poor children are often saved from scurvy by the common use of potatoes. If potatoes are excluded and only the bread and butter diet given scurvy, sooner or later, is exceedingly likely to manifest itself.

To sum up this paper, I will submit that (1) the characteristic symptoms of the so-called acute rickets, viz. the special limb affection and the cachexia, with or without sponginess of gums, are not due to rickets at all but are truly scorbutic.

(2) That the anatomical basis of the limb affection is sub-periosteal haemorrhage, and that this haemorrhage probably accounts for some of the anaemia.

(3) That the disease may occur in rickety children, and perhaps in them more readily than in non-rickety children, but that the amount of rickets may be almost nil.

(4) That although the disease tends spontaneously in many cases towards a slow but complete recovery, marked improvement often follows a vigorous and especially an early antiscorbutic treatment.

(5) That the treatment recommended is—locally, during the acute stage wet compresses and avoidance of movement, at a later period careful shampooing and douches; internally, the use of raw-meat juice, fresh milk, and orange juice, or of some other fresh raw vegetable, and from the first the access of as much free air as is possible.

(6) That the use of the term acute rickets should be abolished for these cases, and that of infantile scurvy substituted, the special note of which, as distinguished from adult scurvy, being the greater incidence of the disease on the bones.

(7) That with regard to the hand feeding of infants it seems probable that the so-called 'infant foods' cannot be trusted as sole aliment for any lengthened period, however useful they may be as adjuncts.

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THE ISOLATION AND IDENTIFICATION OF VITAMIN C

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At the time when Barlow's activities were gradually impressing upon medical opinion the identity of infantile scurvy with the adult form of the disease and the fact that their common source lay in errors of diet, the science of nutrition was beginning to reveal the importance of the presence in some natural foods of small quantities of unknown substances essential to life (Lunin[10]), which were later to become known as vitamins. Neither the clinician nor the experimental investigator could then foresee the magnitude of the problem to which these observations were leading. The horizon, however, definitely widened when Grijns[19], in continuation of Eijkman's work, suggested that the cause of beri-beri was a dietetic deficiency.

That scurvy was caused by the consumption of an incomplete diet was by then almost universally acknowledged and consequently the discovery that the origin of another disease could be traced to faulty nutrition was not unique. The method of approach, on the other hand, which led to the discovery of this 'deficiency disease' was distinctly novel and was to become instrumental in the progressive activity soon to follow in this field of research.

As far back as 1869, Forster, working in Voit's laboratory at Munich, was investigating the function of mineral constituents in the diet and published his results in 1873[17]. In the course of this work he administered to pigeons a diet consisting of caseinogen and starch previously purified so as to remove the inorganic constituents with the result that the experimental birds developed symptoms, including opisthotonus, which were characteristic of what is now recognized as avian polyneuritis. The onset of this condition Forster ascribed to a deficiency of salts, not an unexpected conclusion considering the object of the inquiry and the trend of nutritional research at that period. The attention of the experimenter was then mainly focussed on the mineral constituents of the diets with the object of demonstrating what is now taken for granted, namely, their indispensability. It was, in fact, research of this character which was gradually yielding results destined to lead later to the equally gradual formulation of the vitamin hypothesis. Some twenty years after Forster's description of his experiments, similar observations, this time to be correctly interpreted, were independently made by Eijkman[12, 13, 14]. The prevalence of beri-beri amongst Europeans in the Dutch Indies impelled the Dutch Government to send out a commission in

1886 to inquire into the cause of this disease. Eijkman was one of the assistants of this commission and remained behind after its departure to pursue the inquiry. During his investigations an epidemic broke out amongst his experimental hens. The symptoms displayed were similar to those described by Forster. Eijkman, however, soon satisfied himself that these symptoms were of polyneuritic origin and he named the disease 'polyneuritis gallinarum.' Furthermore he was struck by the similarity of this disease with that of beri-beri in man which he was studying. With characteristic shrewdness, Eijkman instituted an inquiry into the origin of the epidemic. It was then revealed that during the time when the birds were suffering from polyneuritis they were fed on rejected boiled polished rice from the kitchen of the military hospital which the 'diener' of Eijkman's laboratory (under civil administration) utilized on grounds of economy. Fortunately the cook in the military hospital was replaced by one who was less favourably disposed to civilian activities and the perquisite was stopped. On the consequent re-introduction of unpolished rice the epidemic amongst the birds ceased. The cause of the epidemic was plainly suggested by this coincidence. Further work of Eijkman and his successors, and above all of Grijns[19], showed first that the deficiency of the polished-rice diet was not due to the lack of inorganic constituents and secondly that human beri-beri also resulted from the one-sided consumption of decorticated rice from which a dietetic factor had been removed in the milling. Such striking observations could not remain dormant for long.

It is outside the scope of this paper to trace the numerous and interesting investigations on experimental polyneuritis and beri-beri that followed. The lines on which these researches were pursued made circumstances propitious for the discovery of the production of experimental scurvy and as is usual in human progress they found their man. Axel Holst[31, 32] in an endeavour to find out whether polyneuritic diets were able to produce the disease in animals other than birds, observed that guinea pigs developed a pathological condition distinctly different from polyneuritis. This condition Holst and Frölich were able to identify with scurvy. Further point was lent to the problem when they found that the scorbutic symptoms failed to appear when the deficient diet was supplemented by antiscorbutic foods. Five years later they published[33] a full record of their brilliant experiments, which will always remain classical.

The results of this pioneer effort were not long in being put into practice. The provisioning of the troops in the great war, especially in certain zones, presented possibilities of 'deficiency disease' making its appearance. This necessitated the careful assessment of the vitamins in raw and treated food-stuffs. Holst and Frölich's work was extended with great rapidity and methods were improved and made quantitative in nature (Chick and Hume[6, 7]). Moreover, laboratory observations were utilized and found to be of value in the actual prevention and cure of scurvy in the field. The ground was now prepared for the task of the biochemist.

Chemical studies.

It will be easier to appreciate fully the development of the chemistry of vitamin C by recalling the appearance of the problem in the

early stages of the inquiry. The only method of establishing the presence or absence of the vitamin was the biological method which, as is well known, is time consuming and often subject to untoward delays and complications. The choice of reagents that could be used in the chemical study of the vitamin was limited since toxicity had to be considered in connection with the testing. Negative results could not always be interpreted as such, because the inactivation of more or less concentrated preparations in the process of manipulation had to be considered owing to the labile nature of the vitamin. These difficulties were to a great extent overcome as the chemical properties were gradually revealed by patient research. In fact, the concentration of the active principle was only achieved in intermittent stages as its conditions of inactivation became known. Although the fractionation and the study of the chemical and physical properties occurred concurrently, for the sake of clarity the two branches of research will be treated separately and not in chronological order.

The citrus fruits were always considered as specifics against scurvy. This fact was confirmed by experiments showing the lemon and the orange to belong to the most potent natural sources known at the time. It was only comparatively recently that the mango (Perry and Zilva[42]), paprika (Svirbely and Szent- Györgyi[49]) and the anterior lobe of the pituitary (Gough and Zilva[18]) were discovered to be markedly more active. The lemon particularly appeared to lend itself to chemical work since the bulk of the solid matter in its juices, namely, the organic acids, was found to possess no antiscorbutic activity. The removal of this inactive residue yields in consequence a solution the potency of which can be raised by concentration at low temperature and pressure. Such preparations were found to be active when tested on animals and human beings (Harden and Zilva[21], Harden, Still and Zilva[20], Zilva[62, 64]). After removal of the acids from lemon juice it was shown that the sugar contained in the residue could be fermented without impairing the activity of the juice (Zilva[63], Lepkovsky, Hart, Hastings and Frazier[39]). Alcohol precipitated further impurities after which precipitation with basic lead acetate yielded a very active fraction (Zilva[65]). It is now known that these preparations sometimes approximated very closely indeed in activity to that of pure ascorbic acid, but were characterized by instability and, not being crystalline, offered little possibility of chemical identification. Lemon juice is a source from which the crystalline vitamin can be obtained only with the greatest difficulty. Later the process was modified by precipitating the active principle with neutral lead acetate at pH 7·2 (Zilva[67]). Concentrates were also obtained by basic lead acetate precipitation from other plant juices such as swede juice (Zilva[66]) and cabbage juice (Bezssonoff[4]).

Data which afforded some illuminating information on the chemical character of the antiscorbutic factor were obtained by means of diffusion experiments. Holst and Frölich had already proved that the vitamin could diffuse through a parchment membrane, which implied that the active principle was not a colloid or associated with anything in colloidal dispersion.

A technique of differential dialysis devised by Brown[5] offered further possibilities of studying this problem.

Brown's technique consisted in dialysing solutions through collodion thimbles without the application of pressure. By soaking the thimbles in alcohol of various strengths, different degrees of permeability were obtained. Thus a thimble soaked, say in 30 per cent. alcohol, allowed substances of lower molecular dimensions to pass through, whilst impeding the passage of larger molecules which could pass through a thimble soaked in stronger alcohol, such as 90 per cent. In other words a molecular sieve with meshes of varying sizes was obtained by regulating the strength of the alcohol in which the collodion was soaked. Applying this technique to the study of vitamin C (Zilva and Miura[73]) it was found that membranes which permitted a free passage to substances of small molecular dimensions such as sodium chloride retained the antiscorbutic factor during a period of three to four days. Only thimbles through which semicolloidal substances, such as dyes, passed allowed the vitamin to dialyse. In extending this investigation it was demonstrated (Connell and Zilva[9]) that the active principle diffused through membranes of somewhat lower permeability than that which permitted the passage of dyes, the size of the active molecule appeared to be not far removed from that of a hexose and further the rates of diffusion of the antiscorbutic factor, of the nitrogenous residue and of the reducing sugars were different.

These results indicated that vitamin C was in all probability nitrogen-free and that the size of the active molecule whether associated or free was that of a hexose. On the identification of the vitamin nine years later, it was found indeed to be a hexose derivative.

As mentioned above one of the greatest difficulties in the fractionation and purification of the vitamin was its lack of stability and it was therefore, of paramount importance to throw some light on the mechanism of this inactivation.

Holst and Frölich emphasized in their pioneer work the instability of vitamin C. They found, for instance, that certain vegetables (white cabbage, dandelion) lost much of their potency in the process of cooking. The juices were even more thermolabile and deteriorated quickly also at room temperature. Acid juices, on the other hand, were more stable both when heated and when stored. They demonstrated that this increase in stability was due to acidity since citric acid extracts of cabbage juice were markedly more stable than the untreated juice. Further work on the subject indicated that the loss in activity incurred during heating could not be due entirely to thermal degradation. Delf[11] observed that when swede and orange juices were heated at temperatures above 100° C. in a closed autoclave the loss of activity was much reduced. She, therefore, suggested that the rate of destruction of the vitamin was affected either directly by retarding oxidation or indirectly by the production of stabilizing bodies. That the former was the case was proved simultaneously by two workers as an indirect outcome of different investigations. Hess[26] and Hess and Unger[27] found that the addition of hydrogen peroxide to raw milk under conditions which prevented the growth of bacteria had a deleterious influence on the antiscorbutic activity of the milk, from which it was concluded that this destruction was due to oxidation especially as they also found that neutralized milk or tomato juice loses antiscorbutic value on shaking in air. The other line of evidence emerged from the study of the effect of ultraviolet light. It was found that when the ozone generated

by the lamp did not come in contact with the antiscorbutic solution the activity was hardly impaired (Zilva[58]). On the other hand, contact with ozone even at room temperature or the passage of air for several hours destroyed the vitamin. When the decitrated lemon juice, used in these experiments, was boiled in an atmosphere of CO_2 for two hours no marked diminution in the antiscorbutic activity could be recorded (Zilva[59, 60]). It, therefore, became clear that oxidation was the main factor concerned in the destruction of the antiscorbutic factor. Even heating decitrated lemon juice in an autoclave for one hour at 40 lb. pressure (143° C.) destroyed only about one-half of the vitamin (Zilva[69])—a loss most probably due not to thermal degradation but to the presence of very slight traces of oxygen in solution.

The destructive effect of oxygen on vitamin C having been established it became clear that this reaction was controlled by another factor, namely, the hydrogen-ion concentration. The observations of Holst and Frölich that the antiscorbutic activity of extracts disappeared in alkaline much quicker than in acid solution could now be co-ordinated with the oxidative process of inactivation. It was shown (Zilva[61]) that decitrated lemon juice when made $\frac{N}{20}$ alkaline and exposed to the air at room temperature lost about 80 per cent. of its potency in half an hour. On the other hand, when the same solution was kept in the absence of air no loss in activity took place. Moreover such drastic treatment as aspirating air through a boiling solution of lemon juice as acid as pH 2·2 greatly delayed the destruction of the active principle. These experiments, therefore, established the fact that the destructive oxidation of the vitamin was deterred in acid and greatly accelerated in alkaline solution. Other factors conducing to the oxidation of vitamin C will receive later reference.

Another characteristic property of active solutions was their power of reducing a number of reagents. Bezssonoff[2, 3] found that vegetable extracts containing the vitamin reduced phosphomolybdotungstic acid (Folin reagent for phenols). Even concentrates from which many impurities had been removed were observed to reduce ammonical silver nitrate and to decolorize potassium permanganate in the cold (Zilva[63, 65]). These results were so striking that it became evident that they occupied a pivotal position in the scheme of vitamin C research. An early attempt to correlate these two reactions with antiscorbutic activity (Connell and Zilva[8]) failed to establish a parallelism. Both these reagents, however, are reduced by a great number of substances and consequently this negative result could not be considered as final. A more specific reagent phenolindophenol* was eventually found which made it possible to determine conveniently the reducing capacity of antiscorbutically-potent substances with precision (Zilva[68]). The reagent is decolorized by antiscorbutic solutions in the process of reduction and by this reaction the connection between reduction and vitamin activity was investigated. Two main features came to light in this inquiry. One was, that although a certain parallelism between antiscorbutic activity and reduction existed, there were, nevertheless, marked deviations. The second observation showed that when decitrated lemon juice was oxidized with indophenol and administered to the

* Substituted indophenols fulfil the same object.

experimental animals immediately, the major part of the vitamin activity was retained by the solution. If, on the other hand, the oxidized antiscorbutic was allowed to remain for about twenty-four hours before dosing it became almost inactive (Zilva[69]). The writer's interpretation of his results was that vitamin C itself did not reduce indophenol but that the decolorization of the indicator was due to a reducing substance closely associated with the active principle, which tended to prevent oxidation.

About this time the hope of isolating the vitamin was realized but in a manner which had not been foreseen. Moreover, the antiscorbutic character of the substance thus isolated was not appreciated until some years later. Engaged in an investigation on the part played by the adrenal cortex in biological oxidation with the ultimate aim of elucidating its function in the renal system, Szent-Györgyi[50] isolated from the cortex a highly reducing hexose derivative—hexuronic acid. This compound he found also in vegetables and fruits where it appeared to function in connection with peroxidase systems, thus associating the adrenal cortex with this oxidizing mechanism. Amongst other observations he recorded that hexuronic acid decolorized indophenol—a fact which prompted him to suggest that the acid was probably identical with the reducing substance postulated by the writer (Zilva[68]). Professor Szent-Györgyi kindly offered to supply the writer with hexuronic acid in order to test this suggestion experimentally, but unfortunately owing to the scarcity of the material at the time and his subsequent departure from England the matter was left in abeyance. However, another substance isolated from orange juice by Szent-Györgyi, which he thought might be the vitamin (private communication by letter) was in the meantime (June-July, 1928) tested by the writer at Professor Szent-Györgyi's request and was found to be antiscorbutically inactive in daily doses of 3 mgm. and 5 mgm. (cf. Svirbely and Szent-Györgyi[48]).

Not many years elapsed before the chemical identity of vitamin C was established and, as in the case of its isolation, in a manner not expected. Tillmans*, in trying to devise a method for discriminating between natural lemon juice and the artificial product employed 2, 6-dichloroindophenol, it being known that this compound was decolorized by orange juice, with the result that he found that only the fresh natural lemon juice reduced the indicator. In communicating this observation at a meeting in Nüremberg the point was raised whether this reducing capacity had any connection with vitamin C. On investigating this matter further he found[51], as the writer had done before, a certain parallelism between the two properties, but unlike the writer, he was inclined to attribute the two properties to one substance. The writer's observation that decitrated lemon juice retained its antiscorbutic activity after oxidation, Tillmans maintained could be explained by assuming that the substance was reversibly oxidized whilst remaining antiscorbutically

* Whilst writing this review (February, 1935) news reached me of Professor Tillmans' death. I should like to take this opportunity of expressing my sincere admiration not only of his capacity bu' also of his truly scientific spirit.

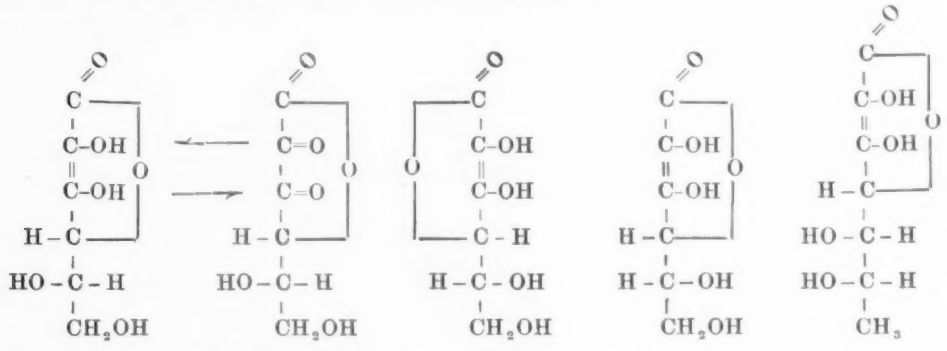
active. In this first stage of oxidation, according to him, the vitamin was more prone than in the original reduced form to destruction by further oxidation. It is of interest to note that Szent-Györgyi[50] had found that hexuronic acid could also be reversibly oxidized but his work was not known to Tillmans in 1930. The similarity, however, between the reducing substance which Tillmans considered to be vitamin C and hexuronic acid was thus indicated then. Later (Tillmans et al., [52, 53, 54, 55, 56]) when he had worked out his thesis in greater detail and became acquainted with the work on hexuronic acid he actually suggested that vitamin C was probably identical with it. Very soon after the appearance of Tillmans' last series of publications, King and Waugh[38, 57] claimed to have isolated a crystalline substance from lemon juice, by the decitration and lead acetate method mentioned previously, which, in their opinion, was hexuronic acid and which was antiscorbutically active. Simultaneously Szent-Györgyi[47, 48] examined an authentic sample of crystalline hexuronic acid from the adrenal cortex and found it also potent.

The antiscorbutic activity of hexuronic acid could not, however, be taken as a final proof that this compound was identical with vitamin C (Zilva[72]). Workers in the vitamin field were particularly reminiscent of precedents in which active crystalline substances owed the particular vitamin potency not to the crystalline compound but to adhering 'impurities.' A similar condition could be visualized in the case of hexuronic acid. Crucial evidence was nevertheless soon obtained which militated against this view. Szent-Györgyi[49] was able to show that the monoacetone derivative of ascorbic acid—under which name hexuronic acid became at this stage to be known—was antiscorbuticallly active but not to the full extent and that the ascorbic acid recovered from it was, on the other hand, fully active. Hirst and Zilva[28] found that when ascorbic acid was oxidized with iodine to its first oxidation product (dehydroascorbic acid) it was almost as active as it was before oxidation. This observation was similar to the one made by the writer[68] when the vitamin in decitrated lemon juice was oxidized with indophenol. By reducing the dehydroascorbic acid, ascorbic acid was re-obtained which was as active antiscorbutically as the original compound from which the oxidation product was prepared. These results strongly pointed to the fact that ascorbic acid was active per se. The alternative explanation that the vitamin was in association with ascorbic acid and could, like it, be reversibly oxidized and regenerated quantitatively was in the highest degree improbable. In view of these facts the writer's hypothesis that the reducing substance and the vitamin were not identical but in close association became untenable and Tillmans' theory was thus shown to be correct. The observation that synthetic ascorbic acid obtained from inactive material was fully active (Reichstein and Oppenhauer[45], Haworth, Hirst and Zilva[24]) supplied the final and incontrovertible proof.

Structure of the vitamin.—As was to be expected a compound of such physiological significance as ascorbic acid could not fail to engage the atten-

tion of carbohydrate chemists. An intensive quest led to the establishment of its chemical structure and the eventual realization of its synthesis. Only the outstanding achievements can be given here in the barest outline.

Of the several structural formulae proposed the one which has found general acceptance is that shown below. This was put forward by Hirst and his collaborators of Birmingham, whose proof of this structural formula was arrived at by the ingenious application of various methods employed in the study of the structure of the carbohydrates[25].



l-ascorbic acid	dehydro-ascorbic acid	*d*-ascorbic acid	*d*-arabo-ascorbic acid	*l*-rhamno-ascorbic-acid
active	active	not active	active $\frac{1}{20}$	active $\frac{1}{8}$

A little later the same formula was suggested independently by Euler and Martius[15], their suggestions being based on indirect analogy with the substance reductone (CHOH:COH·CHO), which resembles ascorbic acid in its property of reducing indophenol. The synthesis of ascorbic acid was soon accomplished independently by Reichstein of Zurich[45] and by Haworth, Hirst and their school at Birmingham[24] from *l*-xylosone by way of the hydrogen cyanide addition compound. As xylosone is difficult to prepare this method of synthesis could not conveniently be applied in the preparation of large quantities of ascorbic acid. New methods have been developed in which the starting material is *l*-sorbose, a sugar which is now readily available in quantity. In Reichstein's method[44] sorbose is converted into its acetone compound and thence into 2-keto-*l*-gulonic acid, from which *l*-ascorbic acid is easily obtained (compare Maurer and Schiedt's transformation of methyl 2-keto-*d*-gluconate into *d*-arabo-ascorbic acid[41]). In Haworth's method[22, 23] the requisite 2-keto-*l*-gulonic acid is produced directly by simple oxidation of *l*-sorbose. By such methods *l*-ascorbic acid can now be produced at an economic price.

The schemes employed in the synthesis of *l*-ascorbic acid were eventually utilized in the preparation of a number of analogues and derivatives, of which some such as *d*-arabo-ascorbic acid (Maurer and Schiedt[41], Dalmer and Moll[10]), *l*-rhamno-ascorbic acid (Reichstein[43], Reichstein, Schwarz and Grüssner[46]) and *l*-gluco-ascorbic acid (Reichstein[43]) have been found to be partly potent, whilst others had no antiscorbutic activity. As a striking example of these latter isomers one may mention *d*-ascorbic acid, the enantiomorph of the fully active *l*-ascorbic acid.

Chemical and physical properties.

The availability of the pure compound made it possible to study its chemical and physical properties in greater detail. The characteristics of the vitamin previously established were fully confirmed. One feature, however, calls for comment. Pure crystalline *l*-ascorbic acid and the other active compounds are perfectly stable in solid condition, a fact which seems at first to be strikingly contradictory to the instability of vitamin C. This apparent paradox can nevertheless be explained. In studying the process of inactivation of the antiscorbutic factor it was found (Zilva[69, 70, 71], Johnson and Zilva[34]) that certain phenolic substances, which are widespread in plant tissues, are subject to spontaneous oxidation giving rise to products capable of oxidizing in their turn the vitamin. In addition, Euler, Myrbäck and Larsson[16] showed that traces of certain metals could catalyse the oxidation of ascorbic acid, an observation which explains why the pure compound becomes slowly inactivated in aqueous solution. Recent work throws further light on this subject. In water carefully distilled from and received in quartz apparatus, *l*-ascorbic acid is exceptionally stable even when this water is previously saturated with oxygen (Kellie and Zilva[36]). This suggests that contact with oxygen in the absence of catalysts does not destroy the activity. The instability of the vitamin in natural juices or in concentrates when exposed to air is evidently due to the presence of various catalytic substances. That mere traces of these impurities may have a deleterious effect on the vitamin is seen from the fact mentioned above that concentrates were sometimes obtained by the writer which, weight for weight, were almost, if not as active, as crystalline ascorbic acid, but lacking the stability of the latter. The natural medium from which these preparations were made, namely, lemon juice, offered great technical difficulties in removing the adhering traces of these destructive impurities which imparted the instability to the vitamin in this condition.

It is significant that in the tissue of the living plant or animal biological conditions are such as to conduce to the stability of vitamin C. Only when the tissue is disintegrated is this balance upset. Since in the natural sequence of things the disintegration takes place through mastication as the food is consumed, no serious loss in antiscorbutic activity can take place before the ingested vitamin is utilized by the organism.

As in natural sources and in concentrates indophenol still remains the most specific reagent for pure *l*-ascorbic acid and its analogues. Nevertheless the specificity is far from being complete, so that this reagent is of doubtful value for detection and determination of these compounds. Since his introduction of this indicator in 1927 the writer had the opportunity of carrying out a critical study of this problem on a large scale, especially

between 1928 and 1933, during which time he and his colleagues were engaged in an extensive inquiry into the vitamin C of natural products. He arrived at the conviction that in spite of the excellent agreement between the biological and the indophenol titration values found in many instances, the latter procedure broke down in unexpected instances in a way which made the general application of the indicator in the assessment of anti-scorbutic potency undesirable, particularly in the hands of the less cautious. For this reason he deliberately abstained from urging the utilization of this reaction only for the detection of the antiscorbutic factor. The same criticism may be levelled at the application of the selective absorption displayed by ascorbic acid in the ultraviolet region of the spectrum for the determination of vitamin C. The biological activity still remains the ultimate criterion for vitamin C. Among the biological methods the prophylactic method yields the most accurate results but is laborious. The curative method in which the test dose is administered to the animals from the tenth to fifteenth day on the basal diet until the thirtieth day when they are killed is almost as accurate and less laborious (cf. Johnson and Zilva[35]). Another biological method—Höjer's method—is sometimes employed. This method is based on the fact that in guinea-pigs on a scorbutic diet there is an early change in the odontoblastic layer of the teeth (Zilva and Wells[74], Höjer[29, 30], Key and Elphick[37]). The advantages claimed for this method, namely the small amount of material required, and the short duration of the test are possessed by the curative method which does not, on the other hand, share the disadvantages of the former. The chief of these are variability in the individual response of the experimental animals, the totally subjective interpretation of the results and the necessity of making histological sections.

In this review the chemical nature of vitamin C only has been briefly discussed. That this vital principle, the absence of which is responsible for the production of scurvy in animals incapable of synthesizing it, may play an important part in the metabolic functions of the animal organism needs little stressing. Nor is it likely that its synthesis and presence in the plant kingdom is without significance. A good deal of sound information bearing on these points which falls outside the aim of the present review has been already obtained in the course of study of the chemical nature of the antiscorbutic factor. The identification of the vitamin naturally quickened the pace of research in this domain, but it is not easy at the moment to assess the true value of many of these latter contributions in an excessively prolific field, especially as some results leave a debatable zone of possible error. Many gaps remain to be filled before a major hypothesis can be formulated. When the time, whether it be close or remote, is ripe for the integration of the essential and established facts in their true perspective, scientific workers might with advantage look back to Barlow's Bradshaw Lecture as a model for clarity of vision, logical exposition and, above all, intellectual probity.

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THE RECOGNITION OF SCURVY WITH ESPECIAL REFERENCE TO THE EARLY X-RAY CHANGES

BY

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Twelve years ago, under the auspices of the United States Children's Bureau, Dr. Martha Eliot undertook the prevention of rickets in a district of New Haven, Connecticut, numbering 12,000 inhabitants. At once it became necessary to have more accurate knowledge than was available concerning the criteria for the diagnosis of early rickets in the x-ray films. Accordingly comparative x-ray and histological studies of the bones of all children dying from any cause in the paediatric service of the New Haven Hospital were begun, and have been continued at the Harriet Lane Home, Johns Hopkins Hospital, Baltimore. Altogether examinations have been made of the bones of 532 children between the ages of two months and two years. In the course of the work scurvy was discovered in a number of patients in whom the disease had not been suspected during life, and in this way it was learned that scurvy was escaping diagnosis. Moreover, as the result of the comparisons of the x-ray films of individual bones with their histological counterparts certain early x-ray manifestations of scurvy were observed, which had either entirely escaped attention previously or else had never received adequate notice in the literature. The case records of scurvy in the Harriet Lane files were then examined in the hope of obtaining further information. Altogether, the clinical and x-ray records in 125 cases of scurvy have been studied, and the present paper is the result. Its main emphasis is on the early x-ray signs of scurvy and their histological interpretation, but it also contains scattered observations of clinical interest and importance.

* Miss Bond is the head of the Social Service Department of the Harriet Lane Home and was kind enough to conduct the investigations in the homes of the cases of scurvy reported in this paper.

The first signs of scurvy in the x-ray films of the bones of the extremities.

The signs of advanced scurvy in the x-ray film have been described by Wimberger[1], McLean and McIntosh[2], Kato[3], and many others. The discussion here is confined to the early changes. The illustrations give far better ideas of them than can be conveyed in words (fig. 1, 2 and 3) and these, with all others later referred to, will be found at the end of this paper. The description now to be given serves both as explanation and legend.

Wrists (fig. 1). (The x-ray films were taken with the forearm supinated.) At the wrists the most common early sign of the disease was a defect of the outer corner of the lower end of the radius. In its earliest development it appeared as scarcely more than a fuzziness of the cortex and the slightest rarefaction of the neighbouring cancellous tissue. The cortex was so thin that it was almost indistinguishable or seemed to be lacking altogether. The general effect was to make the corner appear indistinct (fig. 1 a and k). When the lesion was further developed the defect became definite. It then most commonly took the form of a cleft or crevice just underneath the lattice.* The cleft included the cortex as well as the shaft. It showed various degrees of development in different cases. In some the cleft was so slight as to escape observation until especially looked for (fig. 1 b). In others it extended a short distance into the substance of the bone or even half-way across (fig. 1 m). In still others, the corner had the appearance of having been torn away from the body of the shaft (fig. 1 e, f, g and h). The torn part was the lattice; the tear had occurred through a rarefied zone which could be seen extending beyond the detached fragment. Instead of a cleft, the outer corner was marked in some bones by a triangular area of rarefaction. The cortex adjacent to this appeared extremely thin. The normal contour of the bone was preserved (fig. 1 i and k). In some cases the outer corner appeared rounded and thrust out beyond the outer end of the lattice and greatly rarefied. We have called this phenomenon ' bagging ' (fig. 1 l).

The inner angle of the radius was affected similarly to the outer angle (fig. 1 i), but seems much less liable to injury.

The changes in the ulna were more varied than in the radius. Either corner or both were involved (fig. 1 i, g, and k). The cortex appeared thin or absent and the adjacent cancellous tissue rarefied. The rarefaction was slight and limited to the corner, or assumed a triangular shape and extended some distance into the substance of the shaft (fig. 1 k). A crack or cleft was often present (fig. 1 c and j); or the corner appeared torn off (fig. 1 a and g). The lower end of the ulna was frequently cupped (fig. 1 d, e, g, i, l, m and n); if the cortex which forms the sides of the

* We discuss the lattice at length in connexion with the histology of scurvy. It is sufficient to state here that the lattice is the framework of calcified matrix substance of the cartilage which is responsible for the dense shadow at the end of the shaft. ' Underneath the lattice ' means underneath the dense scorbutic band of shadow which lies across the end of the shaft in the x-ray film.

cup was thin, the appearance in the x-ray film was that of a halo (fig. 1 d and h). Halo formation is certainly not characteristic of scurvy, though it was well marked in a number of our cases. In one case the lower end of the ulna showed a spicule shaped like a thorn protruding from the rim of the cup (fig. 1 o).

When the radius and ulna were viewed together, relationships were noted which seem worth mentioning. In some instances the lattice was torn off at the outer corners of both bones (fig. 1 f). In others it was torn off at the outer corner of the radius and the inner corner of the ulna. In still others triangular zones of rarefaction were present at the outer corners of both bones (fig. 1 i), and in yet others the outer corner of the radius and the inner corner of the ulna were both affected in this way (fig. 1 k). In a number of cases in which the scorbutic process was probably of longer standing, the end of the ulna and the adjacent part of the end of the radius appeared compressed, whereas the outer part of the radius showed a cleft as if pulled apart (fig. 1 d, e, m and n). In an extreme case the lower end of the ulna had obviously been crushed to such an extent that the lattice had been absorbed (fig. 1 e). In another case the lattice had been shifted inwards so that it overlapped the shaft on its inner aspect (fig. 1 m). The carpal and metacarpal bones showed nothing characteristic.

Ankles (fig. 2). (The x-ray pictures were taken in the lateral position.) The early manifestations of scurvy were more frequently noted at the ankles than at the wrists and were of the same general nature. By far the most characteristic and constant change was a defect at the anterior corner of the tibia. The defect took the form of a spot of rarefaction involving both cortex and cancellous tissue (fig. 2 a, b and c), a cleft (fig. 2 d, e, g, h, l, m and o), bagging (fig. 2 f and i), and bagging and cleft (fig. 2 j). As in the case of the radius the cleft varied from a degree at which it was just discernible on careful examination (fig. 2 c and d) to one in which it was most obvious, and extended one-third or one-half the way across the bone. In some instances the corner seemed drawn out to an abnormally sharp point (fig. 2 k). In one the anterior corner appeared cracked off (fig. 2 m). In many the posterior corner as well showed the scorbutic lesion : cleft (fig. 2 a, l and o); bagging (fig. 2 e) and over-extension and pointing of corner (fig. 2 d, f, i and k). It is significant that cleft formation occurred far more commonly at the anterior than at the posterior corner. Because of the super-imposition of the shadow of the fibula the changes at the posterior corner of the tibia were often obscured. In fig. 2 o, epiphyseal separation seemed imminent because of the proximity of the anterior and posterior clefts. The lattice was curved and appeared to rest against the end of the shaft as the rocker of a rocking chair rests against the floor. In fig. 2 b, a cleft must have been present but became obliterated as the result of the compression. In contrast to this, in fig. 2 e, the lattice has not been pressed back, hence the cleft is visible.

The fibula was much less affected than the tibia, but in occasional cases showed clefts at the anterior corner (fig. 2 d), usually occurring in association with similar clefts at the anterior corner of the tibia. In a number of cases the fibula was cupped and either the anterior or posterior angle was drawn to an unusually fine point. The lower end of the fibula in many films was obscured by the presence of the nucleus of ossification of the tibia, or, as already stated, by the tibia itself. The tarsal and metatarsal bones show nothing characteristic.

Shoulders, elbows and knees (fig. 3). (The shoulders were studied only in the antero-posterior position.) The characteristic early lesion was a cleft immediately underlying the lattice at the outer corner of the end of the bone. It varied from a minute spot of rarefaction to a crevice which extended half through the breadth of the bone (fig. 3 a and b). In cases in which scurvy had become more advanced other changes developed, such as cupping of the outer half of the end of the bone and over-extension and pointing of the corners. However, the cleft just mentioned was the only pathognomonic early sign noted.

(The elbows were examined in a position of partial flexion with the forearms supinated. The angle was about 135 degrees. The arm was slightly abducted at the shoulder. The upper end of the radius lay in almost complete supination.) The only positive sign found was a nick at the upper end of the radius in three cases. In two the nick was situated at the inner corner and in the other at the outer corner (fig. 3 c and d). In some cases the lower end of the humerus showed a thin lattice band which was not characteristic of scurvy. It was noteworthy that, with the exception stated, the elbow appeared free from involvement, even though lesions were well marked at wrists and ankles.

(The knee was examined in the lateral view only.) The study was productive of much less of value than in the case of either wrist or ankle. The lower end of the shaft of the femur presents so uneven a surface in the lateral position, that super-imposition blurs the outline. Only in advanced cases were characteristic lesions delineated. The upper end of the tibia was more satisfactory than the lower end of the femur, but not as valuable as the lower end of the tibia or the radius and ulna at the wrists. An early sign at the upper end of the tibia was a cleft between the lattice and body of the bone at the posterior corner. As usual with scorbutic clefts, its size varied from being just perceptible (fig. 3 e) to a crevice extending one-third or more toward the front of the bone (fig. 3 f and g). In some cases a cleft was found anteriorly as well as posteriorly (fig. 3 g). The upper epiphysis of the tibia is shaped like a yachting cap, with the vizor overlapping the tibial tuberosity. (Fig. 3 i, shows complete epiphyseal separation and is included here in order to show what the shape of the epiphysis actually is.) In a number of cases the characteristic change was a spot of rarefaction under the vizor, which made the latter conspicuous and appear to stick out from the front of the bone (fig. 3 e, h and g). It is not certain how specific of scurvy the changes enumerated at the upper end of the tibia actually are, with the exception of the clefts. The upper end of

the fibula was not of much aid, as this bone is too protected by the tibia. In an occasional case it showed slight cleft formation at the posterior corner. The anterior corner was obscured in most of our films by the overlying shadow of the tibia. Because of lack of good x-ray films observations have not been made on the upper end of the femur.

Ribs. These bones are affected in scurvy as in rickets earlier than the bones of the extremities, but the costochondral junctions, which are the sites of predeliction for the disease, cannot be photographed clearly enough in the living child to render them satisfactory for study.

Distribution of the lesions (fig. 4). An x-ray of the arm and leg from one patient has been reproduced in order to illustrate the grouping of the lesions in the different bones and their relation to each other. The signs of scurvy are so characteristic at both wrists and ankles as to be pathognomonic. Those at the knees also seem definite. An unusual lesion at the knee is the minute cleft at the posterior corner of the upper end of the fibula. The absence of evidences of scurvy at the elbow is usual. The impression has been gained that the lower end of the tibia, as seen in lateral view, most commonly shows evidence of the disease. On the other hand, in some children the lower ends of the radius and ulna have exhibited the more striking and characteristic lesions. Characteristic signs have been found in the upper ends of the humeri in x-ray pictures taken to show the chest and, as a result, scurvy has been recognized. Probably antero-posterior views of the knee and ankle would have furnished comparatively early and definite evidences of the disease, had they been available. But it must be remembered that good films of the legs in the extended position are exceedingly difficult to obtain in scurvy on account of the induced pain.

The explanation of the early signs.

Certain growth processes in scurvy which are fundamental to its comprehension must first be discussed. Some are normal, some pathological.

(1) In scurvy calcification takes place in the normal manner. It is inhibited only if rickets is present.

(2) The epiphyseal cartilage continues to produce new cells, that is, it continues to grow, even after the scurvy has developed. Growth in length of the long bones, therefore, keeps on, unless the disease become so severe that even proliferation in the epiphyseal cartilage stops. The practical significance of this for us is that in scurvy the cartilage keeps giving off its framework of matrix substance for the shaft to take over and form into bone.

(3) Osteoblastic activity in the shaft and growth activity in the proliferative cartilage are distinct processes, carried on by different kinds of cells, apparently under different control. Although, then, the cartilage cells divide and growth in length goes forward, osteoblastic bone formation stops* and growth in thickness ceases. This means specifically that new

* Osteoblastic activity may not stop completely in scurvy; it virtually stops, however. New bone may form at scattered points where, presumably, the growth stimulus happens to be great enough to affect the cells even in spite of the inhibiting influence of the vitamin C deficiency.

bone not only no longer forms on the surfaces of old bone, but does not develop on the framework of calcified matrix substance which the cartilage keeps furnishing.

(4) The resorption of bone which was already formed before the scurvy began goes on at an increased rate throughout the skeleton. The histologist finds evidence of this by means of the microscope; the best evidence, however, is derived by inference from the x-ray film, which shows progressive thinning of the shadow cast by the bone, the longer the disease lasts. Destruction of bone, though universal in scurvy, occurs in certain regions much more rapidly than in others, and the regions at which it takes place most rapidly of all are those which in health were the seats of most active growth. Under normal conditions bone is formed far more rapidly at the end of the shaft just under the cartilage than elsewhere, and it is in this region in the bone which suffers from the rarefying process out of all proportion to the rest.

(5) It is most interesting that, though the lamellar and trabecular systems of the bone undergo disintegration in scurvy, as just stated, the framework of calcified matrix substance which the cartilage keeps furnishing to the shaft, relatively speaking, escapes. Normally this is in greater part destroyed almost as soon as formed. The practical meaning is that the framework of calcified matrix material, as such, keeps accumulating and increasing in size at the end of the shaft.

(6) The capillaries of the shaft leak plasma and also here and there permit the passage of red blood cells in small or, sometimes, in very large numbers. The result is that capillary hæmorrhages occur at various points in the substance of the bone, and sometimes large haemorrhages develop either in the marrow cavity or under the periosteum. It is known that the walls of the blood vessels become permeable in scurvy, and unable to hold their contents. It is suspected that the circulation of nutrient fluids is also impaired, and the osteoblasts and bone corpuscles no longer receive adequate nourishment. But of this possibility no direct knowledge has been obtained.

(7) The marrow cells migrate away from the ends of the bones where growth is occurring rapidly, leaving the supporting connective tissue framework exposed to view. This connective tissue framework is termed in German, 'Gerüstmark,' or marrow framework, as translated into English.

These are the pathological processes which are at work in scurvy. The first six are the ones responsible for the characteristic phenomena in the x-rays; the last is one of the cardinal histological signs of scurvy, but does not influence the x-ray picture. It is now possible to attempt to give understandable explanations for the x-ray changes. The scorbutic lattice will first be described.

Perhaps the most characteristic phenomenon in the x-ray film in cases of scurvy and the one earliest to appear is the dense shadow lying across the end of the shaft. This shadow is cast by the scorbutic lattice (fig. 5, 6, 7 and 8). In brief outline, the lattice is the framework of calcified matrix substance of the cartilage. It is bare, since it is devoid of any covering of bone. Present in embryonic form in normal growing bone in the provisional zone of calcification of the cartilage, it reaches pathological proportions in scurvy because, while its formation continues, its destruction ceases. It casts a dense shadow because of its great content of lime.

In scurvy, as under normal conditions, the capillaries keep invading and destroying the columns of cartilage cells as fast as the latter mature, but leave untouched the supporting calcified framework of matrix substance. Accordingly, the cartilage keeps leaving behind, as it grows, its framework of calcified matrix material. The continuous formation and giving off by the cartilage of this framework of calcified matrix substance is a normal growth process, which is preserved in scurvy unless the disease becomes most severe. Under normal conditions the framework of calcified matrix substance is destroyed in its greater part as soon as, stripped of its cartilage cells, it is reached by the invading capillaries of the shaft. This destruction takes place close to the junction of cartilage and shaft. In the healthy infant perhaps four-fifths or nine-tenths of it is destroyed almost immediately after its formation. Only here and there in the lines of strain constituent parts of the framework escape destruction, become covered with encasements of bone as the result of the activity of the osteoblasts, and made over into the trabecular system. Under the influence of scurvy the framework of calcified matrix substance of the cartilage is either not destroyed at all, or else is most imperfectly destroyed.* This cessation in the orderly destructive process is a pathological condition which occurs in scurvy and, also, congenital syphilis. Bone is a living tissue, as already pointed out, and like other living tissues, is dependent on the steady flow of nutrient material, and cannot withstand the conditions imposed by scurvy. Undoubtedly the reason why the framework of calcified matrix substance escapes destruction in scurvy is that it is a dead tissue.

Normally the osteoblasts rapidly encase the parts of the framework of calcified matrix substance which escape destruction with layers of bone. Because of their inability in scurvy to cover over any part of this framework, the framework remains bare of bone. This breakdown in bone building in this particular place is a most characteristic abnormal phenomenon not only in scurvy but also congenital syphilis. It has great practical importance. Bone is a fibrillar tissue; without reinforcement with covering layers of bone the framework of calcified matrix substance has little strength and fractures easily. The framework of calcified matrix substance is exceedingly dense. Its density is readily understandable as soon as it is recalled that in the original cartilage in which it was formed its walls were separated from each other only by the columns of cartilage cells. In other words, in the aggregate there is a great mass of it. Moreover, because it is pure matrix material without cells, it probably takes up lime salts in greater concentration than bone. The bone corpuscles themselves do not take up lime salts. Its content of calcium per unit of volume must be much greater than bone whose trabeculae are, relatively speaking, few in number and widely separated. Undoubtedly a subjective factor is concerned in the dense appearance of the lattice shadow in scurvy. The faintness of the shadow cast by the rest of the bone, and in particular

* The even regular physiological destruction stops. Irregular focal destructions take place, in particular where fractures have occurred.

by the zone of rarefaction lying next door, makes the lattice shadow seem denser than it actually is*.

The lattice stains a deep blue with haematoxylin and shows no cellular structure, except where cartilage cells have been entrapped and preserved from contact with the capillaries. Bone, in contrast, stains pink with eosin and shows its contained bone corpuscles. The two can be easily distinguished from each other by histological methods, and the identity of the lattice with the calcified matrix substance of the cartilage established beyond a doubt. In figures 5 and 9, the lattice is beautifully shown, and with its black appearance and dense ' thicketty ' structure forms a marked contrast to the sparse thin trabeculæ of the cancellous tissue.

The idea that in scurvy, and also in congenital syphilis, the lattice of calcified matrix substance is responsible for the heavy band of shadow at the end of the shaft and for the peculiar liability of the end to fracture is new. Years ago Fraenkel[1], in his monograph on the x-ray manifestations of scurvy, ascribed the bright band of shadow to the ' Trümmerfeldzone.' The ' Trümmerfeldzone,' according to him, was the region of fracture. The shadow was produced by the fragments of the matrix material and adjacent trabeculae of bone, which were packed together with blood clot lying between. This idea has been accepted without question by the various writers on the subject since that time. In reality, blood clots cast no more shadow than soft tissues in general. It is not the compressed fragments of the fractured lattice which cast the shadow, but the lattice itself. In some cases the fragments are compressed; in others they are scattered or few in number. The compression factor tends to be offset by the rarefaction factor, because rarefaction seems to set in rapidly where fractures have occurred.

The zone of rarefaction (fig. 9 and 10) lies at the end of the shaft next to the lattice on the shaftward side of the latter. It is one of the classical x-ray signs of scurvy, and is always sought for, whenever scurvy is suspected. As described by Wimberger and other writers, it extends completely across the bone, but, if the disease has not progressed far in the bones, it may be only partially developed, or not present at all. The zone of rarefaction is not, therefore, a constant sign of scurvy, and cannot be regarded as being essential for the x-ray diagnosis. When fully developed, the zone of rarefaction is as broad as, and usually much

* In the cases of advanced scurvy which have been studied the proliferative cartilage has been abnormal. The cells have been small, their formation into columns irregular and the quantity of matrix substance excessive. The scorbutic lattice is formed in the cartilage and its pattern and the thickness of its structure are determined in the cartilage. The lattice was most irregular in the cases of advanced scurvy reported here and its structure in places was much thicker than normal. The abnormal thickness in the lattice structure was also a factor in making the shadow cast an especially heavy one. We have not dared to say that scurvy affects the growth of cartilage, making it abnormal, as it does bone, because of the difficulty in eliminating the possibility that rickets, also, was present in these advanced cases and affected the cartilage. We are, however, inclined to think that scurvy does affect the cartilage, making the matrix framework more irregular and heavier than normal. The affection of the cartilage in this particular way is another reason why the scorbutic lattice casts so heavy a shadow.

broader than, the lattice. It is sharply bounded on the lattice side by the dense band of the latter; on the shaft side, however, it does not have a well-defined margin, but merges with the shadow of the shaft. On the shaft side, also, its development is often irregular, since it may extend into the shaft substance further in some places than in others. The rarefaction zone may be as conspicuous in its way as is the lattice or, on the other hand, be so poorly defined as to escape observation. In most advanced cases the zone of rarefaction may be so maked in the skiagram as to make the epiphysis with the lattice seem entirely separate from the shaft, without even cortex left to join the two together. Like the lattice, it is broader at the fast-growing ends of the long bones than at the slowly-growing ends, and may be visible in the former and not in the latter. In many of the films used for this study, the zone of rarefaction was entirely absent, or only partially developed. The spots of rarefaction (fig. 1 g and i; fig. 2 c) and the clefts (fig. 1 d; fig. 2 h and l) in the first cases actually represent local, probably early developments of the rarefaction zones.

When the zones of rarefaction are studied under the microscope, it is found that the trabeculae of bone are thin, and many of them show signs of surface disintegration. They are not only thin, but are widely separated from each other, obviously because intervening trabeculae have been removed. Around many of the trabeculae are swarms of osteoblasts and similar groups of cells mark places where the trabeculae formerly were. Often in the centre of the groups of cells trabecular fragments are found. The marrow cells have largely or entirely gone from the spaces between the trabeculae. Scattered sprinklings remain. The connective tissue framework of the marrow which is revealed to view as the result of the departure of the marrow cells resembles loose embryonic tissue. Capillary haemorrhages are almost always present (fig. 11) and large haemorrhages may be present (fig. 6). The cortices bounding the rarefaction zones usually are reduced to shell-thickness and in places may be lacking altogether. On the outer and inner surfaces of the cortices are usually found many osteoclasts, and osteoclasts also are scattered in the regions of the trabeculae.

The fractures of the lattice (fig. 6, 8, 12, 13) are conspicuous in the histological preparations, but are invisible in the x-ray films, though their presence can often be inferred in the latter. The zone of rarefaction, on the contrary is much more conspicuous in the x-ray film than in the histological preparations; indeed, on examination of histological preparations with the microscope, it is often a cause for surprise that the region should have appeared so rarefied in the x-ray film. As in the case of the rarefaction zone, fracture may extend all across the bone, giving rise to true epiphyseal separation. On the other hand, it may extend only part way across or may occur at points widely separated from each other. The fractures take place almost always through the lattice and are situated most commonly close to its junction with the bone. On examining sections under the microscope it seems astonishing that the lattice should have given way instead of the greatly rarefied trabeculae of the shaft immediately adjacent, because the latter are so thin and

widely separated, whereas in contrast the lattice is thick and abundant. Though, as already stated, the fractures most commonly take place in the lattice close to its meeting points with the bony trabeculae, they may occur through the middle portion and sometimes they involve the bony trabeculae as well. Fractures do not occur through the lattice immediately beneath the cartilage. Thus, when the epiphysis separates from the diaphysis it always carries some and usually the greater part of the lattice with it.

When the lattice is the seat of extensive fracture the microscope shows its fragments lying in all directions. It evidently shatters, as might be expected of an extremely brittle substance, like glass or china. The fragments may appear as rounded or quadrilateral masses or as splinters. In some cases they are pressed together; again one fragment is found impaling another or several fragments are impacted into one large mass. Around and between the fragments it is usual to find masses of fibrin and in some cases recent haemorrhage. In the regions where fractures have occurred great quantities of cells, evidently osteoblasts, are found which surround the broken fragments like swarms of bees (fig. 14). In many cases these cells seem to have settled thickly on the fragments and the fragments seem in process of disintegration. Where fragments have been jammed together, the blue-staining homogeneous material has changed to a granular detritus which stains pink with eosin. Many giant cells are found in the regions of the fractures, but do not seem to be the chief agents which are bringing to pass the destruction. When the fractures are of less extent the same picture obtains, but is more circumscribed.

Before leaving the subject of fractures, attention must be called to the frequency with which they occur. They are present in the fast-growing ends of the long bones in every case in which the x-ray picture shows a well-marked lattice and must be numerous long before epiphyseal separation occurs. Experience would indicate that in scurvy breaks occur at this point and then at that point and keep multiplying until the end of the bone becomes so weakened that it gives way entirely. The idea that the disintegration of the lattice began so early, advanced so insidiously and was so universal was a new one. Of course, it is understood that as the result of sudden strain the lattice may shatter completely across in a moment.

The spots of rarefaction at the corners of the bone (fig. 15, 16, 17, 18, 19, 20, 21, 22, 23) present microscopic pictures such as might be expected from the descriptions already given. Where ' corner ' spots of rarefaction appear in the x-ray films, the cortex is found to be much thinned and in some places it has disappeared altogether. The cortex always shows fracture, and about the points of fracture rarefaction processes seem to be in full operation. The trabeculae of the adjacent cancellous tissue show signs of disintegration. Large areas are entirely devoid of trabeculae. In these one finds clumps of osteoblasts marking the spots where the trabeculae formerly were and perhaps in the middle of them trabecular remnants in the form of a pink-staining granular detritus. Between the trabeculae connective tissue is found. In some

places this connective tissue has a loose structure and resembles embryonic tissue (the supporting connective tissue framework of the marrow); in other places, particularly along the cortex, the cells are quite closely packed together, as in the fibrous marrow of rickets. Haemorrhages may or may not be present. The reason for the appearance of rarefaction in the x-ray picture is the reduction in size, or even partial absence, of the cortex and in the number and size of the trabeculae. The rarefaction may extend into the lattice.

The typical clefts, cracks or crevices of rarefaction at the 'corners' of the ends of the shafts have not been studied histologically, for the reason that none of the infants autopsied showed well-marked examples. The impression is gained from the x-ray pictures that the bone substance has been pulled apart at the site of the cleft, and it is expected that evidence of trauma in the soft tissues as well as in the trabeculae will be found. From the examination of the spots of rarefaction at the corners just described, it is practically certain that any evidence of trauma would be limited to the osseous elements and that the soft tissues would have stretched and would show no evidence of injury. It would be anticipated that in the areas embraced by the clefts the cortex would have disappeared or been reduced to extremely thin shell-like fragments of bone and that the trabeculae would have entirely disappeared or been represented by residual fragments or detritus surrounded by masses of osteoblasts. The marrow cells would have disappeared and connective tissue would fill in the area. Strands of fibrin would be found running through it which was in process of invasion and organization by the blood vessels. Haemorrhages might be found or pigment from previous haemorrhages.

'Bagging' of the corners in the x-ray film is best understood through examination of the accompanying illustrations (fig. 24, 25, 26, 27, 28 and 29). In 'bagging' the essential condition is the atrophy or fragmentation of the cortex. The loss of cortical support permits the soft tissues to be squeezed outwards when they are compressed as the result of impaction of the shaft against the epiphysis with fragmentation of the lattice. The 'bag' cover is the periosteum.

Over-extension and pointing of the corners is related to 'bagging'; this can readily be understood from the illustrations (fig. 30, 31). When this phenomenon is present in the x-ray film, the lattice will be found to have developed around the side of the proliferative cartilage. The absence or great reduction in the cortical shadow just under the lattice and the rarefaction of the adjacent cancellous tissue throws the lattice into a sharp relief in the x-ray film and makes the latter appear as a long drawn-out corner.

The rarefaction of the shaft, upon which so much emphasis is placed in the x-ray studies of scurvy, is not an early sign of the disease and is not pathognomonic, since it occurs in other illnesses in which the

bones undergo rarefaction. In some of the present cases it was extremely marked (fig. 5). The shafts of the long bones are merely cylinders of bone filled with soft tissue. The soft tissue does not cast shadows of any consequence. The ' cortical shadows ' in the x-ray film are cast by the sides of the cylinder, which lie parallel to the rays and hence offer thick obstacles for the x-ray to penetrate. The shadows of the ' bone proper ' between are nothing more than the superimposed shadows of the front and back walls of the cylinder, which lie at right angles to the rays; in other words, they represent merely a double thickness of cortex. In scurvy the current teaching is that the cortices appear thin and the bone between presents a ground-glass appearance. Some students have even regarded this appearance as specific. The cortex in scurvy does become thin and the thinness comes out in the projections of the sides. The intervening bone does not present a ground-glass appearance, if the rarefaction has reached an advanced development; it is not peculiar to scurvy. The ground-glass quality is caused by an increased porosity of the cortex, and the increased porosity is the result of absorption of the walls of the tunnels in the cortex which transmit the nutrient blood vessels. These tunnels or apertures in the cortex become larger and hence the cortex actually does become more porous. The thinness of the cortex allows a small degree of porosity to show in the x-ray film.

The subperiosteal haemorrhages which constitute such a well-known sign of scurvy in the x-ray film do not, strictly speaking, come into the scope of this article. Subperiosteal haemorrhage develops only when the involvement of the bone has reached an advanced stage. The subperiosteal haemorrhages originate at the ends of the bones and extend towards the middle. They are the result of the fractures of the cortex and lattice at the end of the shaft. Presumably, when the end of the bone gives way, periosteal vessels are torn and the blood escapes under sufficient pressure to lift up the periosteum. McLean and McIntosh have shown that in scurvy the periosteum becomes loosened, so that it can be separated from the underlying cortex with a minimum of force. Their observations suggest that extravasated blood can burrow beneath the periosteum much more easily in scurvy than in health. From the x-ray point of view it is interesting that the subperiosteal haemorrhages do not become outlined and hence visible until about ten days after treatment is instituted. Ossification in the periosteal membrane covering the clot does not begin until the vitamin C deficiency is corrected. An interval is required before it progresses far enough to produce visible changes in the x-ray film.

Discussion.

Rickets is a disease of the entire bone; scurvy, practically speaking, is a disease of the growing ends, and the disturbances to which it gives rise are essentially limited to the growing ends. The weakness imparted to the end of the bone by rickets causes the end to bend; the weakness

from scurvy causes it to break, and the finer changes in the x-ray film, such as have been described, are all due to weakening and breaking. Spots of rarefaction and clefts in certain characteristic regions have been described, for example, in the outer rim of the lower end of the radius and in the anterior rim of the lower end of the tibia. Unfortunately the variety of views in these studies was not complete; in particular, views of the ankle and knee in the antero-posterior position were lacking. If x-ray examinations had allowed the study of the shaft ends from all sides, doubtless other favourite sites for lesions would have come to light. The examiner, in search of early signs of scurvy, does not need to know the favourite sites, however, if he will make use of his knowledge of the modus operandi of the disease. He will then look for the scorbutic lattice and evidence that the lesions in question are in the lattice or adjacent portions of the shaft. In particular he will investigate the peripheral region of the end of the shaft, since this is where strains seem first to produce their effect and early lesions develop in consequence. Lesions such as have been described at the periphery of the lattice, especially if they are multiple, are characteristic of scurvy. The only other disease which causes a lattice to form is congenital syphilis. The characteristic lesions which have been found in scurvy have never been seen in congenital syphilis, although the lattice often fractures completely across in syphilis.

The sites of election for lesions in the lattice are the points where it is especially apt to be subjected to stress and strain. It has been assumed that the anterior rim at the lower end of the shaft of the tibia is a point of especial selection, because of the pull of the weight of the foot in the recumbent position. Similarly, the outer rim of the lower end of the shaft of the radius tends to give way because of the strain imposed by the weight of the hand when the arm is in mid-pronation, a hypothesis which is further borne out by the frequent occurrence together of cleft formation (pulling apart) at the outer side of the radius and evident compression of the end of the ulna and adjacent part of the end of the radius (fig. 1, m and n). A cleft forms in the outer part of the upper end of the humerus because of the pull of the muscles in abducting the arm and supporting it in the abducted position. The fibula is little affected because it is splinted by the tibia. Fractures of the lattice are exceedingly common in the ribs because of the strain of the respiratory movements. The impression has been gained that the fracturing force required to injure the scorbutic lattice, when the latter is well developed, is extremely slight. It is believed that the lattice, unsupported by covering layers of bone, has not much more strength than so much chalk.

There is another factor which determines the vulnerability of the end of a bone in scurvy, and that is the rate of growth. Scurvy, like rickets, affects the end of a bone in direct proportion to its rate of growth. The more rapid the growth, the greater the lattice production, and the broader the lattice becomes, the greater the liability to break. The exemption from x-ray signs of scurvy of the ends of the bones meeting at the elbow

joint is explained by their slowness of growth, as also in the case of the small bones of the hands and feet. There has, however, been found with the microscope crumbling of the shell of lattice at the posterior corner of the head of the olecranon process of the ulna, though it grows most slowly (fig. 32 and 33). It is attributed to pressure from the weight of the arm resting on the elbow. The middle ribs become especially fragile at their anterior ends because of their exceedingly rapid growth. It is suggested that the rationale in the development of the early lesions is as follows :—As the result of the deficiency in vitamin C, healthy growth of bone ceases, the scorbutic lattice forms, the adjacent trabeculae of bone and the enveloping cortex become thin and the end of the bone correspondingly weak. The factor of strain is supplied. The part of the weakened end which bears most of the strain gives way. Bone cannot withstand strain in scurvy; first, all power of repair through the production of new bone is lost as the result of the specific action of the disease; second, strain stimuli, which, under normal conditions, would cause new bone to form, seem to have a reverse action and hasten the destructive process. Rarefaction proceeds rapidly. Broken lattice or bone fragments are absorbed entirely. The weakness advances and extends. Other trabeculae further within give way. A vicious circle is established; the process advances with increasing rapidity until it reaches through the entire breadth of the bone.

The scorbutic deformity of the rib.

In the normal infant the enlargement of the costo-chondral junction is greater on the inside of the thorax than on the outside. In rickets and scurvy the disproportion becomes even more pronounced. Inasmuch as only the external surface of the costo-chondral junction is accessible to clinical examination, it alone will be considered. The palpatory phenomena in cases of moderate severity will first be described, and afterwards in cases in which the disease has reached its most advanced stage of development.

In some moderately developed cases the examining finger passes along the rib in a straight line until it reaches the chondral junction, when, without encountering any ridge, it slips into a little hollow not more than 2 cm. wide, formed by the cartilage. The hollow lies just beyond the end of the rib, as if, as is actually the case, the cartilage at its beginning were bowed slightly inwards (fig. 34 b and c). If the examiner palpates in the reverse direction, that is, from cartilage to rib, the hollow is better felt. As soon as the finger crosses the hollow, it encounters a barrier formed by the end of the rib, which may be so marked as to make it seem as if the cartilage had fallen back slightly, leaving the end partially uncovered. In other cases a slight variation is encountered in that the actual line of junction of rib and cartilage is elevated into a ridge, which the palpating finger is conscious of surmounting just before slipping into the depression (fig. 34 d). In still other cases a further variation is found in the form of a hollow on the rib as well as on the cartilage side of the junction (fig. 34 a and e). In these circumstances the line of junction

forms quite a sharp ridge, from the summit of which the adjacent sides of the depression slope away like the sides of a roof. If the infant is not fat the hollows in the costal cartilages, as well as the scorbutic rosary, are visible and appear as grooves or gulleys, bounding the elevations on their inner side. The scorbutic costo-chondral junction feels hard and whatever deformity is present seems sharply limited to it. The rib

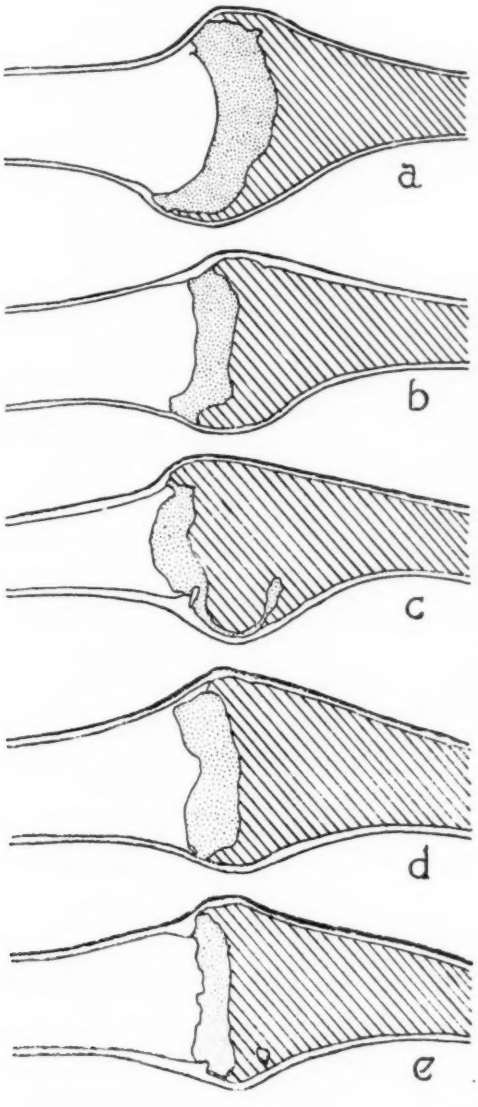


FIG. 34.—Drawings from sections of sample ribs from five infants proved to have scurvy at autopsy. The sections were taken in the transverse direction. Consequently, the upper contour of each costo-chondral junction represents the outer surface and the lower the internal surface. The hatched portion represents the rib, the white, the resting cartilage and the stippled the proliferative cartilage. Descriptions of the different types of deformity which these drawings illustrate have been given in the text.

maintains its normal arch in scurvy. The costal cartilages of the middle ribs normally do not continue in the exact lines of the ribs, but are deflected slightly inwards. In scurvy the slight normal angles formed either remain unaltered or else become actually increased. The result is that the scorbutic deformity, then, is situated at the apex of an angle, feels angular, and acquires an additional prominence in that way. The deformity is most

marked in the fifth, sixth and seventh ribs. In the fourth it is not sufficiently well developed to be characteristic, and in the eighth, ninth and tenth is not so typical.

The opportunity of carefully examining the costo-chondral junctions has occurred in only two infants, in whom the disease had reached its most extreme development. In one, a living infant under the care of Dr. Thomas Cooley in Detroit, the thorax was sunk anteriorly. With each inspiration the sternum and cartilages appeared sucked back towards the vertebral column, forming a hollow several centimetres deep; with expiration, the hollow suddenly flattened. In this case the junction of cartilage and rib was marked externally by a sharp angle, which in expiration was about 45 degrees and in inspiration became a right angle. In the other infant, seen only after autopsy, the middle group of costo-chondral junctions presented contours such as have just been described. The eighth and ninth ribs, however, showed a true 'bayonet' type of deformity (fig. 35). The plateau of the rib surface suddenly stopped; the palpating finger passed over a ledge and dropped, as it were, to the costal cartilage. This is the only example encountered meriting the term 'bayonet deformity,' and in this case it was limited to the lower true ribs.

In autopsy cases four different pathological conditions have been observed which influence or determine the contour of the costo-chondral junction in scurvy.

(1) In all cases of scurvy in which involvement of the costo-chondral junctions is clinically apparent, the cartilage-rib junction is actually broadened. The disturbance of growth caused by scurvy renders the junction weak. Nature responds by broadening the opposing surfaces of the junction. As the result of the resolution of forces at the cartilage-rib junction, the proliferative cartilage develops new columns of cartilage cells along its periphery and these are thrown out obliquely or even at right angles to the main axis of the shaft. As seen in the single plane of the histological preparation, they radiate out from the sides of the proliferative cartilage fanwise. Inasmuch as the growth of shaft always follows the growth of the cartilage in an obligatory fashion and is really determined by the latter, the shaft keeps developing up along the sides of the proliferative cartilage until it encircles the latter. Ultimately the proliferative cartilage becomes shaped like the head of a mushroom or a knob which the end of the shaft embraces in a cup. In this way the cartilage-shaft junction becomes broadened and the broadening shows itself internally and externally through a ridge or elevation. In some cases of scurvy further broadening of the cartilage-rib junction is due to the weakness of the cortices and lattice which give way with the result that the end of the shaft becomes impacted against the cartilage centrally and the peripheral portions are forced outwards.

(2) Normally, as stated, the costal cartilages of the middle and lower ribs do not continue in the line of the rib, but are bent slightly inwards and also upwards. This change in direction occurs abruptly at the costo-chondral junction. In scurvy this internal bend of the cartilage may become increased, in some cases enormously. As is well known, in cases of severe scurvy the thorax is flattened. The flattening is due to the fact that the sternum and adjacent cartilages occupy a more posterior posi-

tion than in the normal thorax, and this backward position has been caused by a sharper bend at the cartilage-shaft junction. The sharper bend is the result of fracture of the lattice. The increased angle formed by rib and costal cartilage causes the enlargement of the costo-chondral junction to be sharp and angular and to protrude. Incidentally, in this connection attention must be called to the fact that the fracture of the ribs through the lattice, which is apparently so common a phenomenon even in moderately severe scurvy, breaks the continuity of the costal arch and permits false motion with the respiratory movements. In the severe case seen in Dr. Cooley's clinic the cartilage moved on the rib at the seat of the break as if hinged. Even in moderately developed examples of the disease the cartilage must rock slightly to and fro with inspiration and expiration on the broken end of the rib, even though the movement is not apparent. The fact that a rocking movement occurred at the site of fractured lattice during life probably accounts for some of the peculiar features of the histological picture of the fracture region in the rib.

(3) As the result of the fracture of the lattice there may be an internal shift of the costal cartilage on the shaft. This is illustrated in fig. 36. From the study of the direction of the strands of fibrin and blood vessels and the relation of the fragments of the broken lattice to each other it can be seen that the proliferative cartilage has slipped inwards on the shaft. This internal shift would tend to produce a hollow on the cartilage side of the junction and would bring the end of the rib into prominence externally. At the beginning of these studies, it was believed that this shaft accounted for the rare phenomenon of the ' bayonet deformity.' It was found, however, that the shift inwards was either not present at all or was very slight and in the single instance in which the deformity merited the term ' bayonet,' the underlying pathological condition was entirely different.

(4) In the single instance of ' bayonet deformity ' it was the cartilage which was deformed and responsible for the musket-barrel-bayonet relationship. The resting cartilage had been pulled inwards on the proliferative cartilage where the nutrient vessels of the proliferative cartilage, the cartilage canals, enter and the overlapping proliferative cartilage on the outer side had been forced against the resting cartilage. This same bend has been seen in the cartilage in one other case, which was not sufficient, however, to produce a ' bayonet ' deformity. It is believed that this peculiar deformity of the cartilage was the result of the pull of the diaphragm which is attached to the cartilages of the lower ribs. It is possible that the resting cartilage itself is weakened in scurvy so that it bends more easily than normally.

Thus the cartilage-shaft junctions of the ribs in scurvy are deformed in different ways and the fact of differences in contour in different cases or at different levels in the same infant does not seem peculiar.

The explanation for the peculiarities of the deformity of the costo-chondral junction in scurvy is that the rib remains rigid and the weakness is sharply limited to the costo-chondral junction. In rickets (fig. 37) the deformity at the costo-chondral junction owes its peculiarities in large part to the fact that the rib itself becomes weak and bends inwards. In scurvy the grooves at the sites of the costo-chondral junctions or Harrison's grooves so characteristic of advanced rickets, are never

seen. The bony thorax remains firm and retains its normal contour. If any part yields, it is the cartilages and sternum. In advanced scurvy, as in the case cited, the thorax gives in the same way as does the normal thorax when severe inspiratory obstruction exists; it is the lower part of the sternum and the cartilages which is sucked inwards. The maintenance of the rigidity of the ribs, while the cartilage bends is a basic fact in the understanding of the characteristic signs of scurvy at the costo-chondral junctions.

The value of the scorbutic deformity at the costo-chondral junction in the diagnosis of scurvy.

The enlargement of the costo-chondral junction in scurvy cannot be classified as an early sign, though it is probably the earliest clinical sign produced by the skeleton. Of the cardinal signs of scurvy the enlargement of the costo-chondral junction is certainly one of the earliest. But it cannot appear until the bone changes are so advanced that the lattice has time to form and to give way. A blindfolded person palpating the chest of normal, rachitic and scorbutic infants would make many mistakes. The costo-chondral junction of the healthy infant may be so ridged as to suggest scurvy and the hollow in the proximal portion of the costal cartilage may be present, also. Particularly when the thorax is ' square shaped,' the cartilage and shaft form an angle which is quite marked, and the line of junction is thrown up into a ridge similar to that seen in scurvy. In rickets the costo-chondral junction may show characteristics of scurvy. The deformity of the costo-chondral junction constitutes one of the cardinal signs of scurvy. Its great usefulness, however, is to suggest scurvy. Time and again it leads to the discovery of the disease. In rare instances it may be so marked that it establishes the diagnosis. An interne was on a visit of inspection in a distant paediatric clinic. A baby on a stretcher was waiting to be wheeled to the operating room. Mechanically the interne felt the costo-chondral junctions and suddenly realized that a scorbutic deformity was present. He hastened to report. The director of the clinic and he arrived in the operating room to find the surgeon bewildered by the discovery of a subperiosteal hematoma.

The nineteen cases studied at autopsy.

As stated at the beginning of this paper, studies have been made of the bones of 532 children between the ages of two months and two years, dying from a variety of diseases in the wards of the Harriet Lane Home. Among this group of children nineteen have been found, through histological examination of the bones, to be suffering from

scurvy (table 1). In only two of these nineteen children had the diagnosis been made clinically. In seventeen the disease was never thought of as a possibility during life. In the pathological department scurvy was recognized in five of the nineteen cases, and in two additional cases it was suspected. The pathologists, then, in the course of their routine autopsies did not recognize the disease in twelve cases. In most instances death occurred so soon after admission (in one case before the examination was complete) that adequate opportunity for clinical examination was not given. In the majority of the undiagnosed cases the obvious illness (for example, pachymeningitis, pneumococcal meningitis, pneumonia, dysentery) was so severe as to absorb the entire attention and make consideration of additional disease seem superfluous. In some of the cases the scurvy was only slightly developed and not recognizable clinically, though in others it was well developed and in one flagrant. The scorbutic deformity of the rib, which might have given the clue, was passed over as rachitic in several instances. In one instance the physician had suggested scurvy but abandoned the thought when the x-ray department reported that the films showed rickets. The reason that the disease was overlooked on routine autopsy examination was undoubtedly that not one of the pathologists happened to have a special interest in diseases of the bone in children. These experiences have had a special importance because they have awakened the consciousness that scurvy had been occurring more frequently than had been realized and had been escaping diagnosis. The discovery of these cases had an unsettling effect. Previously scurvy had been considered easy to recognize. Now it is believed that even among these 532 autopsy cases there must be still other cases of scurvy which have not been recognized. Earlier examinations were performed before the examiners were trained in the recognition of the disease and it should be noted that the histological signs do not become unmistakable until the disease has been at work for some time in the skeleton. In this respect scurvy is so different from rickets which usually clearly declares itself plainly from the beginning. The incidence of rickets in the same series has been approximately 27 per cent.

The other data brought out in the study of this group of autopsy cases are not important. It is perhaps interesting that in five cases the age was five months or less and that in one it was three. Hess[5], in his book on scurvy, states that the youngest age at which he has found the disease was four-and-a-half months. Perhaps a noteworthy fact is the association of scurvy with the major illnesses. It has been looked for in connection with digestive disturbances, failures in nutritional anaemia, dysentery, etc., but, quite illogically, not as an accompaniment of lobar pneumonia, meningitis, etc. Great difficulty was experienced in deciding in regard to the presence or absence of an associated rickets. In nine out of the nineteen cases histological examination made it certain that rickets was present, in four left the matter in doubt and in six indicated

TABLE 1.

INFANTS DYING IN THE HARRIET LANE HOME IN WHOM SCURVY WAS PROVEN BY SPECIAL HISTOLOGICAL STUDY OF BONES.*

Case	Sex	Colour	Age in months	Clinical Diagnosis	Pathological Diagnosis	Rickets	Scurvy diagnosed clinically	Scurvy diagnosed at autopsy
A. S. 559	M.	B.	10	Scurvy; Rickets; Sickle cell anaemia; Diarrhoea with acidosis and dehydration.	Scurvy; Rickets; Sickle cell anaemia; Lobular pneumonia.	+	+	+
R. W. 587	F.	W.	3	Pachymeningitis	Pachymeningitis	−	−	−
M. S. 601	F.	B.	5	Prematurity; Miliary tuberculosis.	Tuberculosis	−	−	−
J. W. 654	F.	B.	6	Diarrhoea with dehydration; Rickets.	Ulcerative enteritis; Scurvy.	+	−	+
R. S. 988	F.	B.	11	Prematurity; Lobular pneumonia; Dehydration, acute.	Pneumonia; Scurvy (?).	Doubtful	−	(?)
J. W. L. 1027	F.	W.	6½	Pneumonia; Dehydration, acute; Acidosis.	Pneumonia; Scurvy.	−	−	+
A. P. 1135	F.	B.	8	Scurvy; Rickets; Dehydration.	Scurvy	Doubtful	+	+
J. B. 1161	M.	B.	5	(Twin) Dysentery.	Dysentery	−	−	−
M. B. 24	M.	W.	5	Pneumonia; Rickets.	Pneumonia	−	−	−

* Professor S. B. Wolbach, of the Department of Pathology of Harvard University, very kindly examined the histological preparations in this series of cases and either confirmed or established the diagnosis of scurvy.

TABLE 1—continued.

Case	Sex	Colour	Age in months	Clinical Diagnosis	Pathological Diagnosis	Rickets	Scurvy diagnosed clinically	Scurvy diagnosed at autopsy
F. B. 198	F.	W.	6	Diarrhoea with extreme dehydration and acidosis.	'History of diarrhoea; Oedema of lungs; Peculiar form of osteochondritis resembling a previous case of scurvy.'	+	–	(?)
E. A. 440	F.	W.	9	Dysentery	Dysentery	Doubtful	–	–
G. H. 449	M.	B.	6	Diarrhoea with dehydration and acidosis.	Pneumonia (early); 'Healed rickets' (?).	+	–	–
L. T. 468	F.	B.	6	Pneumococcal meningitis.	Pneumococcal meningitis; Rickets.	+	–	–
A. W. 504	F.	W.	7	Otitis media; Pyelitis; Dehydration.	Subacute enteritis; Subacute nephritis.	+	–	–
D. M. 50	M.	W.	6	Septicaemia; Pneumococcal pneumonia.	Otitis media; Pneumonia.	+	–	–
C. W. 578	F.	B.	10	Meningitis, pneumoccocus; Rickets.	Meningitis, pneumococcus; Pneumonia; Rickets.	+	–	–
F. R. 581	F.	B.	23	Pneumonia	Pneumonia	Doubtful	–	–
A. B.** 1182	M.	B.	7	Sinusitis	Scurvy	+	–	+
L. T. 369	F.	B.	4½	Meningitis; Meningococcus.	Meningitis	–	–	–

** This child had most extreme scurvy which was not recognized in the out-patient departments of the Harriet Lane Home, the clinic of the Wilmer Ophthalmological Institute, and of the Nose and Throat Department. The diagnosis of sinusitis was made in the Wilmer Clinic. In reality a subperiosteal haemorrhage in the roof of the orbit was present.

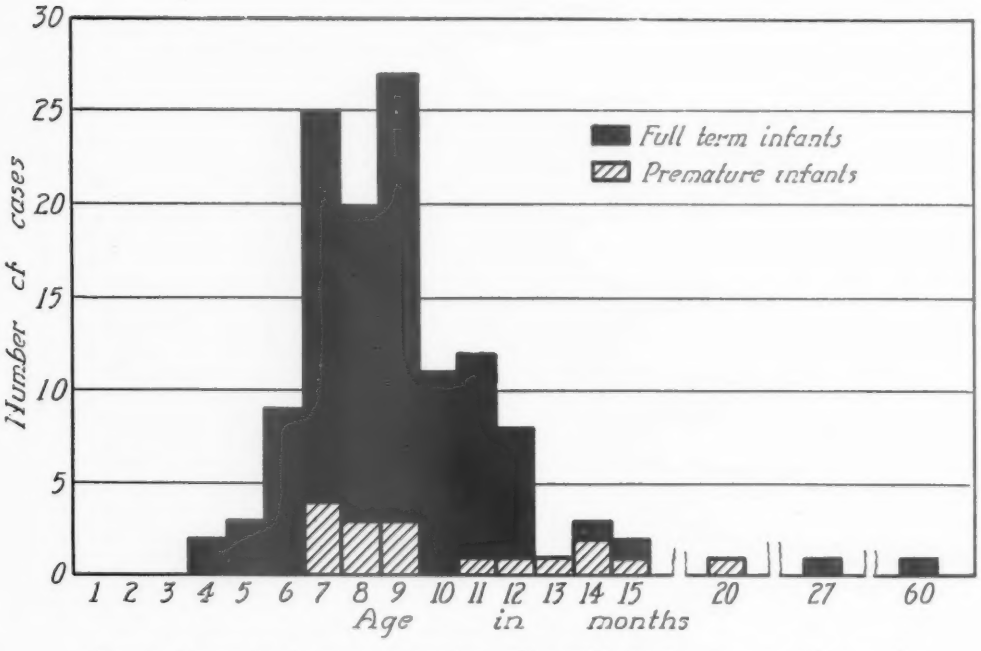
that rickets was not there. The difficulty encountered was that scurvy, if at all advanced, deprives the trabeculae of their osteoid envelopments and so takes away one of the chief means of recognizing rickets. It became necessary, therefore, to rely on the appearance of the cartilage for evidence, and in a number of cases there was doubt whether the changes there were due to rickets or to scurvy. The discussion of the relationship of rickets and scurvy in the present cases and in general is deferred until further studies have been made.

One hundred and twenty-five cases studied clinically*.

As indicated at the beginning of this article, scattered clinical observations were made on 125 cases of scurvy during the course of the x-ray studies. The results of these observations will be considered briefly.

Age at which scurvy became manifest. In the group of 125 cases, the age at which scurvy became manifest ranged from four months to five years. The disease was rare before the age of six months (see chart I)

CHART I.



Age incidence in 125 cases of scurvy. The solid blocks represent the number of full term babies in whom the disease became manifest at the ages indicated; the cross-hatched blocks represent the number of premature babies with scurvy at the same age period.

* This represents the total number of cases of scurvy among 35,000 consecutive admissions to the dispensary and wards of the Harriet Lane Home over a period of eight years.

and the majority of cases (59 per cent.) occurred between seven and nine months of age. This is in accord with the clinical observations of other authors. It is of passing interest that a twenty-seven months old child, who was mentally defective, had had a previous attack, of equal severity, at the age of six months. This was the only child in the series who suffered from two attacks, and both of these are incorporated in the chart. The five-year-old child, however, was, also, mentally deficient.

Diet and other predisposing factors. All of the infants in this group of cases were artificially fed. Most of them were receiving pasteurized milk which was usually boiled in addition. Four were fed on evaporated or condensed milk. Few had begun to take solid food. No case of scurvy in a breast-fed infant has been encountered although a few apparently authentic cases[6, 7] have been reported; in these the scurvy became clinically manifest so soon after birth that they may better be regarded as instances of congenital scurvy. In this connection it is perhaps of interest that one instance of undoubted congenital scurvy has been discovered in the autopsy material examined here. The case is to be reported.

Other factors of minor importance include (1) race, (2) prematurity, (3) twin births, and (4) infection. Of the 125 cases, 75 per cent. occurred in white infants. This is in contrast to the racial incidence of rickets and tetany, which in Baltimore predominates in the coloured child. Inasmuch as the ratio of blacks to whites in the dispensary population at large is approximately half and half, this percentage may be significant. It is possible that more of the coloured infants are at least partially breast fed, or that greater carelessness in feeding results in the accidental introduction of larger amounts of the anti-scorbutic factor. It is also possible that there is a real difference in racial susceptibility. Adequate data for the determination of these points were not available.

There were seventeen premature babies in this group, representing an incidence of 13.6 per cent. Without available statistics as to the exact incidence of prematurity among the total admissions to the Harriet Lane Home, it is impossible to estimate the significance of this figure. It seems, however, as though it represented a fairly high percentage. The premature babies did not develop the disease at a younger age than the full-term babies (see chart I).

Twin births in this series numbered seven. In three instances, only one of the pair was affected. This suggests a difference in individual susceptibility. In one instance, however, the other twin had died six weeks previously of pneumonia and was reported to have had some tenderness of the legs at the time; in another, the more vigorous twin had occasionally received orange juice and vegetables while the scorbutic twin had con-

sistently refused them; in the third instance, one twin had been receiving orange juice for a week, when scurvy developed in the other from whom the orange juice had been withheld on account of diarrhoea. It is possible that the twin who escaped scurvy did so only because the anti-scorbutic regime was started just in time to stave off manifest symptoms of the disease. With regard to the other two pairs, both twins were affected simultaneously in one instance; in the other instance, one twin developed the disease two months earlier than the other. It was stated that both of these were receiving the breast in addition to artificial feedings until two-and-a-half months before scurvy developed in the first twin. This again suggests a difference in individual susceptibility, but it seems more probable that most of the breast milk, during the period of mixed feeding, was taken by the twin who was temporarily spared. In the case of twins, an economic factor may contribute to the development of scurvy, since the cost of anti-scorbutic substances for two is naturally twice that for one.

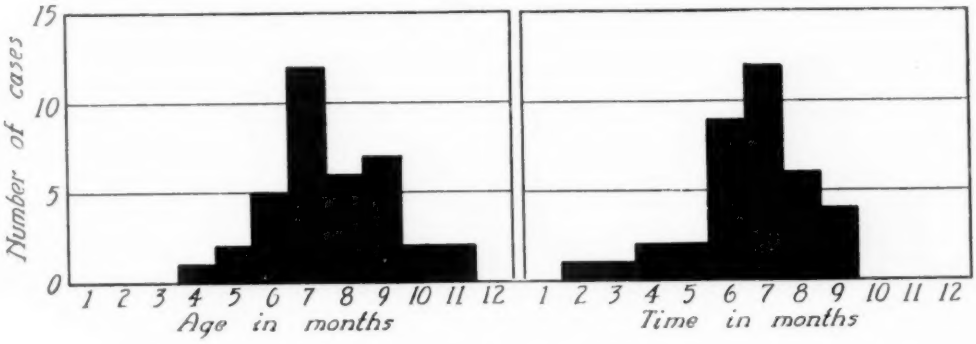
The importance of infection as an etiological factor in the production of scurvy cannot be estimated from this study, although in several instances, it seemed to bear some relationship to the onset of symptoms, at least as a precipitating factor.

Time required for the development of scurvy. It was not possible to determine this in all cases, because of the inaccuracy of the records, since mothers, having previously been advised to give orange juice, often conveyed the impression that they were doing so, quite irrespective of the truth, while the examiners just as frequently failed to check their veracity in spite of obvious discrepancies. In 37 of the cases, however, the time required for the development of manifest scurvy could be estimated with a fair degree of accuracy as there was exact information regarding the period of breast feeding and the use of anti-scorbutic substances. Only one of these patients had received any orange juice at all, and with him it had been discontinued for a known length of time. In these cases, then, the time required for the development of scurvy was computed by subtracting from the age at which the scurvy was diagnosed the duration of symptoms and the period of breast feeding. On the basis of these calculations, the time required varied from two to nine months. There was only one case, however, in which it developed in as short a time as two months. In the majority of instances ($55\frac{1}{2}$ per cent.) it required from six to seven months (chart IIb). The age incidence of these cases is indicated in chart IIa and they are tabulated in detail in table 2.

In the older literature on adult scurvy, it is found that in sailors the disease frequently developed in from four to six weeks and rarely required

more than two months. Lind[8], in his ' Treatise on Scurvy,' described two cruises in which ' the scurvy began to rage after being a month or six weeks at sea ' and another in which ' after leaving the coast of Mexico, in less than seven weeks at sea, the scurvy became highly epidemic.' One is immediately confronted with the problem as to why so much more time is required in the infant than in the adult. Although some authors[9] believe that the infant under five months of age is able to synthesize the anti-scorbutic vitamin it seems more logical to explain the difference on variations in the degree of deprivation. The diet on which the sailor developed scurvy in the eighteenth century was often completely lacking in vitamin C, whereas, in the milk that is fed the infants of to-day, traces probably remain, even though most of it is destroyed by pasteurization.

CHART II.



a. Age incidence of 37 cases of scurvy in which the time required for the development of the disease was known. (There was one premature baby in the seven months' group.)

b. Time required for the development of scurvy in 37 cases. (One that developed in two-and-three-quarter months is charted as three months; one in four-and-three-quarter months is charted as five.)

Seasonal incidence. The question of seasonal incidence was investigated on the chance that it might throw further light on the etiological factors concerned in the development of scurvy. Analysis of the entire group of 125 cases showed that the greatest number for any single month occurred in September (21 per cent.), while more than a third of the total number occurred in September and October together. A more detailed analysis was made of the above 37 cases, in which the duration of conditions conducive to scurvy was known, since in them it could be shown over what period the scurvy was developing as well as the time at which it became manifest. The results of this analysis are presented graphically in chart III. Here again the greatest number of cases occurred in September (22 per cent.), while 40 per cent. occurred in September and October together. It is clear from the chart, that in Baltimore, it is during the summer months that scurvy is generally ' brewing ' with a sudden peak in the incidence of manifest cases in the early fall. This is in direct contrast to the seasonal incidence of rickets, and suggests that season as such is not directly responsible. Indirectly it may affect the

TABLE 2.

THIRTY-SEVEN CASES IN WHICH THE TIME REQUIRED FOR THE DEVELOPMENT OF THE DISEASE WAS KNOWN.

Sex & Race	Age months	Weight lb.	Ht. in.	Time of breast feeding	Symptoms and Duration.	H/T**	Month of onset ***	Time required for scurvy to develop	X-ray changes	Ca	P
										mgm.	per cent.
M—W	7	—	27	0	Pain knees flexed 4 wk.	+/4	Sept.	6 mth.	Well developed		
F—C	7½	14	—	0	*Cried when handled 3 wk.	+/4	July	7 mth.	Well developed + Healing rickets		
F—W	9½	14½	—	1 mth.	Blood in stools 2 wk. Pain 1 wk.	O/2	Feb.	8 mth.	Well developed		
M—C	7	19	—	0	Pain, rt. leg 3 wk. ; left leg 1 wk.	O/O	Nov.	6 mth.	Well developed		
M$_t$—W	9	—	—	1 mth.	Screamed when knees moved 1 wk.	—	Feb.	7¾ mth.	Slight		
M—W	4¾	15¼	—	1 mth.	One foot tender 1 mth.	O/O	Dec.	2¾ mth.	Well developed		
F—W	8	13	20	0	Cried when legs moved 3 mth.	O/O	May	5 mth.	Long standing		
M—W	8½	19¼	—	4 d.	Legs tender 1 wk. Bleeding gums.	+/4	Sept.	8 mth.	Well developed		
F—W	8	18½	—	3 wk.	Gums bruised 5 wk. Fretful 3 wk. Arms and legs tender 10 d.	+/5	Sept.	6 mth.	'Typical'		
F—W	9	—	—	1 wk.	Cried when touched 4 d.	+/2	Oct.	8½ mth.	Definite		
M—W	10¼	18¾	24	1 mth.	Pain, left leg 1 wk.	+/5	Mar.	9 mth.	Marked	10·2 after treatment	5·9
M^p—C	7	—	—	0	Disliked movement left leg 2 d.	—	Oct.	7 mth.	Definite (four plates)		
M—W	6½	15	—	6 wk.	Knees drawn up 2 wk. Fretful.	O/2	Oct.	4½ mth.	Well marked		
F—W	9¼	13½	28	2 wk.	Diarrhoea; pain in legs 3 wk.	+/2	Aug.	8 mth.	Well developed		
M—W	7^3	13½	27½	0	Legs drawn up 6 d.	+/8	Sept.	7½ mth.	Well developed	9·5 5 d. after treatment	5·9
M—W	8½	17	—	0	Pain, right leg 3 d.	+/?	Aug.	8¼ mth.	Well developed		
F—W	5½	10½	—	3 mth.	Cried when handled 10 d. Retrobulbar haemorrhage. Occult blood in stools.	O/O	July	2 mth.	Marked 'at least 2 mth.'		
F—W	8½	17¼	—	2 wk.	Screamed if legs touched 3 d.	O/2	June	8 mth.	Long standing		
M—C	9½	—	—	0	Vomiting, irritable, legs flexed 3 wk. Bl. nose and stool. Petechiae on abd.	+/2	Apr.	9 mth.	Definite	8	2·9

p = premature
t = twin

* Symptoms followed trauma
** H = Haemorrhages into gums
T = Teeth

*** Onset of manifest symptoms

TABLE 2.—CONTINUED.

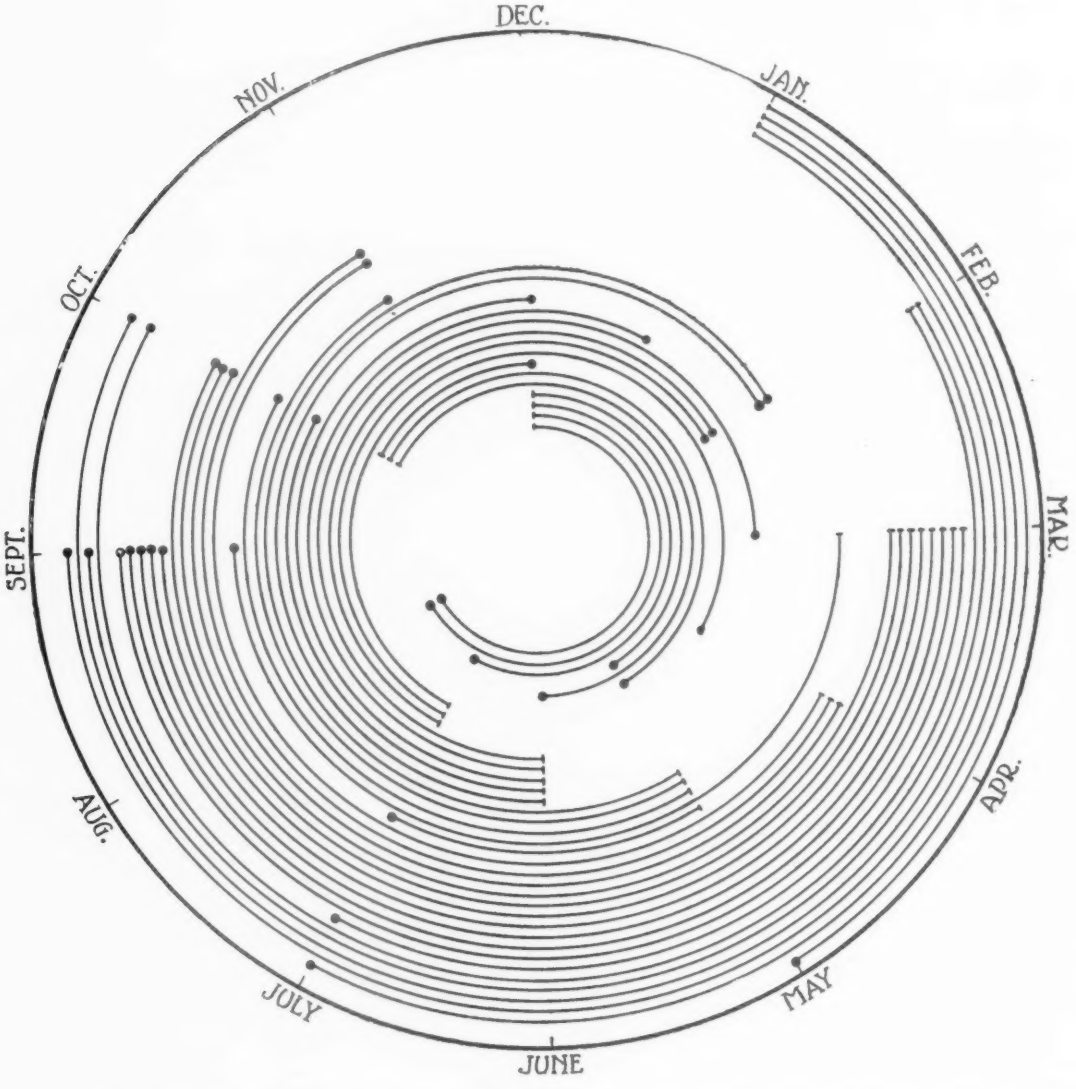
Sex & Race	Age months	Weight lb.	Ht. in.	Time of breast feeding	Symptoms and Duration	H/T**	Month of onset ***	Time required for scurvy to develop	X-ray changes	Ca mgm.	P per cent.
F—C	7	13½	—	0	Pain in legs 3 d.	O/O	May	7 mth.	Marked. + Rickets		
M—W	7½	15¼	--	0	*Swelling rt. knee & ankle 2 d.	+/+	Jan.	7½ mth.	Definite	9·5	4·8
M—C	8	15	—	1 mth.	Joints tender. Bl. gums 3 wk.	+/4	Dec.	6¼ mth.	Well marked		
F—C	13	12	25	0	Screamed when touched 2 mths.	O/O	July	4 mth.	Marked		
M—W	8	13	—	2 wk.	Sickly 1 mo. (Early changes in X-ray then) Bl. gums later	—	Sept.	6½ mth.	Well marked		
F—W	9½	18	—	2 wk.	Pain 2 mth.	+/2	Nov.	7 mth.	Advanced		
M—W	7	14¼	—	2 wk.	Pain in legs 1 wk.	O/2	Sept.	6¼ mth.	Early changes		
M—C	7¼	13¾	—	3 mth.	Cried when picked up & arms raised 2 wk. Pain in legs later	+/1	May	4¼ mth.	Definite. + Marked Rickets		
F—W	8	15	—	0	Screamed when legs touched 1 wk.	+/+	Nov.	7¾ mth.	Early		
F—C	6	13¾	—	0	Pain rt. leg 5 d.	—	July	6 mth.	Relatively early		
F—W	10	16	—	5 d.	Fretful. Screamed 2 wk.	O/8	Oct.	9¼ mth.	Well developed		
F—W	7½	9	22	0	Cried when touched or moved 3 wk.	O/?	Oct.	6¾ mth.	Well developed		
F—W	10	13	—	7 wk.	Rt. leg sore 3 wk.; then left	O/O	Oct.	7½ mth.	Definite	14 after 1 week of treatment	4·8
F—W	10¾	12	25·2	few d.	Pain in legs 1 mth.; later in shoulders	O/O	Feb.	9½ mth.	Marked	9 3 d. after adm.	2·8
F—W	7	19	—	0	Cried when moved 10 d.	—	Sept.	6¾ mth.	Well developed		
F—W	8	11	—	15 d.	Did not want to be touched 3 d.	+/+	Feb.	7½ mth.	Moderately developed		
F—W	12	18	29	5 mth.	Cried when legs moved 1 mth.	+/6	Oct.	6 mth.	Well developed		
M—W	7½	14¼	—	1 mth.	Cried when legs moved 1 wk.	O/O	Sept.	6 mth.	Well developed		

*Symptoms followed trauma *** Onset of manifest symptoms

** H = Haemorrhages into gums
T = Teeth

situation in two ways, through (1) the cost of oranges, which is the source of vitamin C commonly employed in Baltimore, and (2) the frequency of diarrhoeal diseases in hot weather. Because the cost of

CHART III.



SEASONAL INCIDENCE IN 37 CASES OF SCURVY. The black dots indicate cases of manifest scurvy occurring during the different months of the year. The arc leading to each dot indicates the period during which conditions conducive to scurvy existed, in other words, the months during which no antiscorbutic was received.

oranges is higher during the summer months, which is not the season for citrus fruits, it proves inhibitory to some and oranges are consequently omitted from the diet while no substitution is made for them (as by tomato juice). In other instances, the occurrence of diarrhoea may lead to the postponement or discontinuation of the use of orange or tomato

juice, which, through oversight, it is not started or resumed when the intestinal disturbance is over. It is possible, also, that diarrhoea interferes with the absorption of vitamin C when it is supplied.

First symptoms and signs. 'Any way you lay him is the way he lays. If you lay him on his side, he makes no effort to move or nothing. It looks like most of his trouble is from the hips down.' That, in the words of a mother, typifies the clinical picture of scurvy! As a general rule, the symptoms of scurvy appear abruptly. Pain and tenderness of the extremities, or symptoms referable to pain, such as disinclination to move, crying when handled, drawing up of the legs, 'rheumatism,' gave the first evidence of the presence of the disease in 115 (92 per cent.) of the cases, and was ultimately present in all but four. Over and over again the uniformity and prominence of this complaint made a strong impression. The pain was occasionally (twelve cases) initiated by trauma and was usually accompanied by irritability and fretfulness. In ten cases, there was also enough swelling to attract the mother's attention and to figure in the complaint offered by her. In one instance fretfulness was the only symptom mentioned. Haemorrhages into the gums furnished the initial complaint in only five instances, although they were present in forty-six. They were not present in any instance in which there were no teeth, and in 20 per cent. of the infants with teeth they were also lacking, even though scorbutic lesions were well marked in the skeleton. It can be stated with certainty on the basis of this study that when haemorrhages are found in the gums, the signs of scurvy in the skeleton will be well developed. In one case, the appearance of blood in the stools antedated the onset of pain by a week. Its presence was noted in two other instances. Haematuria, usually microscopic, was occasionally found. Epistaxis occurred in three instances, but not as the initial complaint. Petechial haemorrhages were extremely infrequent and retrobulbar haemorrhage occurred only once.

There was a complete lack of parallelism between the duration of symptoms and the apparent duration of the disease process as evidenced by the x-ray pictures. Well-developed scurvy was frequently present in the skeleton when there had been symptoms for only a few days. In one case, in which there were as yet no symptoms, but in which well-marked scurvy was discovered by x-ray, reference to a set of x-rays taken four-and-a-half months previously indicated that it was already present at that time!

Since, then, there is this long latent period during which scurvy may be manifest in the skeleton without recognizable clinical symptoms, attention is attracted to the possibility that less specific prodromal symptoms may precede the others. Many authors describe, as premonitory signs of scurvy, such symptoms as anaemia, disinclination to eat, failure to gain weight or to grow in length. Anaemia was not consistently present in this group of cases, even when there was evidence that the scurvy must have existed for some time. Loss of appetite was mentioned rarely, and then only as an accompaniment of the other manifest symptoms.

Undernutrition was also an inconstant finding. A third of the infants, irrespective of the apparent duration of the scurvy, were of normal weight or above. Slight undernutrition characterized another third, while the remaining third showed marked degrees of undernutrition. There was no real basis for attributing this directly to the scurvy. The length was recorded in only twenty-four instances. Although half of these infants were undersized, this number included seven premature babies, so that this data cannot be regarded as significant. In a few instances it was noted that the baby had ' looked badly ' or ' seemed sickly ' for a few weeks before the pain or disinclination to move was apparent. Definite fretfulness and irritability, though frequently mentioned among the early symptoms, rarely preceded the notice of pain, and were undoubtedly attributable rather than antecedent to it. One child, who was being seen regularly in the out-patient department during the four-month period when scurvy (in retrospect) is known to have been present, was gaining weight steadily and at each visit it was noted that ' feedings are well taken.' It would appear from this study that scurvy, like latent tetany, may, and usually does, from the symptomatic standpoint become suddenly manifest. No explanation can be offered for this sudden appearance of symptoms, excepting in those few cases in which trauma seems to have produced them, probably by precipitating subperiosteal haemorrhage or epiphyseal separation at sites already prepared for them. The suddenness of the disappearance of symptoms under treatment has always been mysterious. Marked improvement, in every instance, was evident within a day or two after the institution of treatment.

In conclusion, it may be remarked that there are no early signs of scurvy. The slight x-ray changes described in this paper enable the diagnosis to be made by x-ray examination of the skeleton somewhat earlier than previously. The scorbutic deformity of the rib is useful as a means of recognition of the disease when well developed. The chief reliance, however, must still be on the symptoms and of these, pain and tenderness in the legs are the most important. It is possible that, in the future, more careful questioning of the more observant mothers will give some indication of more definite premonitory signs. Every infant, known not to have received anti-scorbutic substances over a period of two months, should be held under suspicion. It must be hoped that the numerous studies now in progress in various parts of the world on the metabolism of ascorbic acid will reveal some simple way for the early recognition of the disease.

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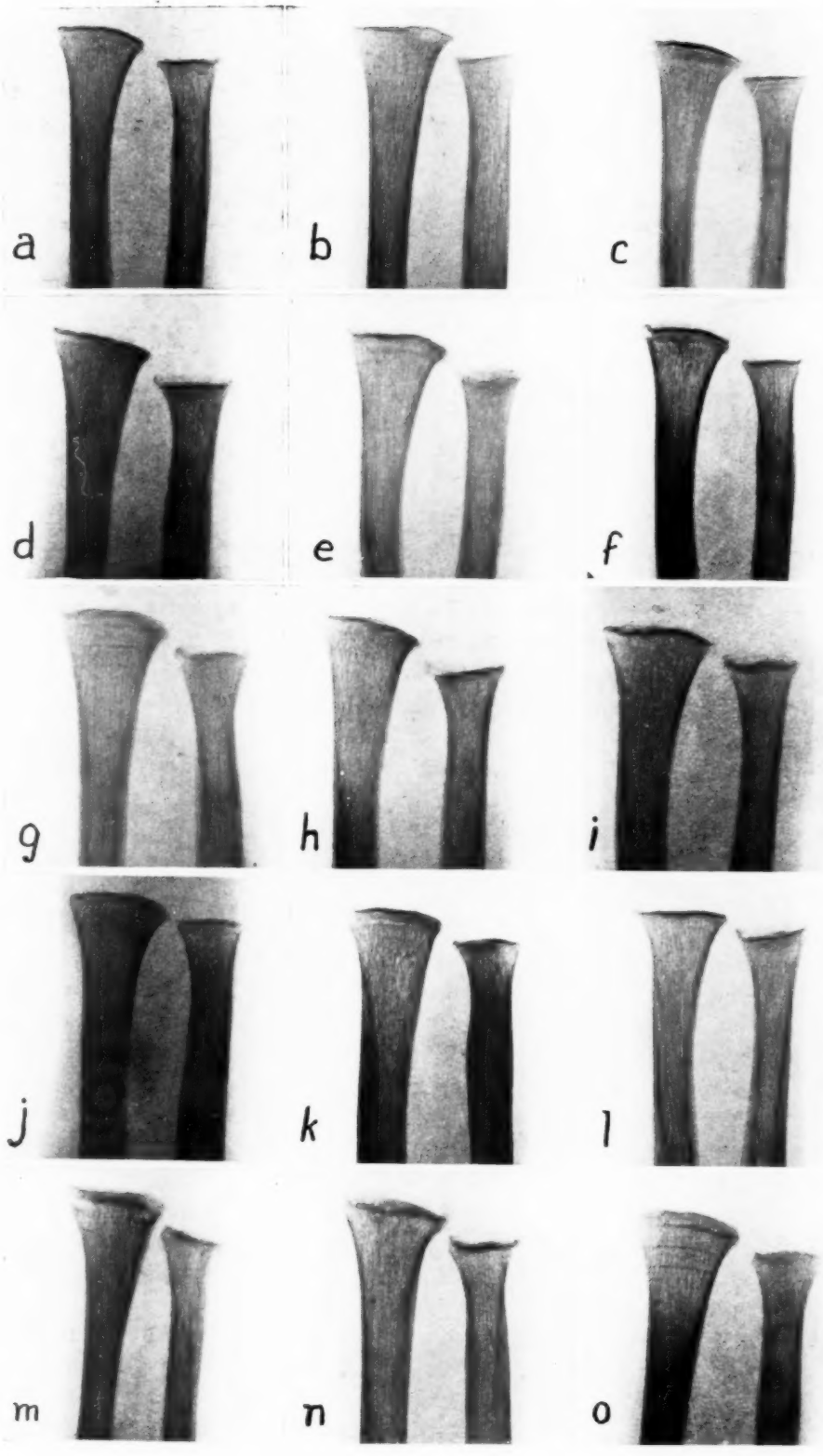

FIG. 1.—For explanation see text.

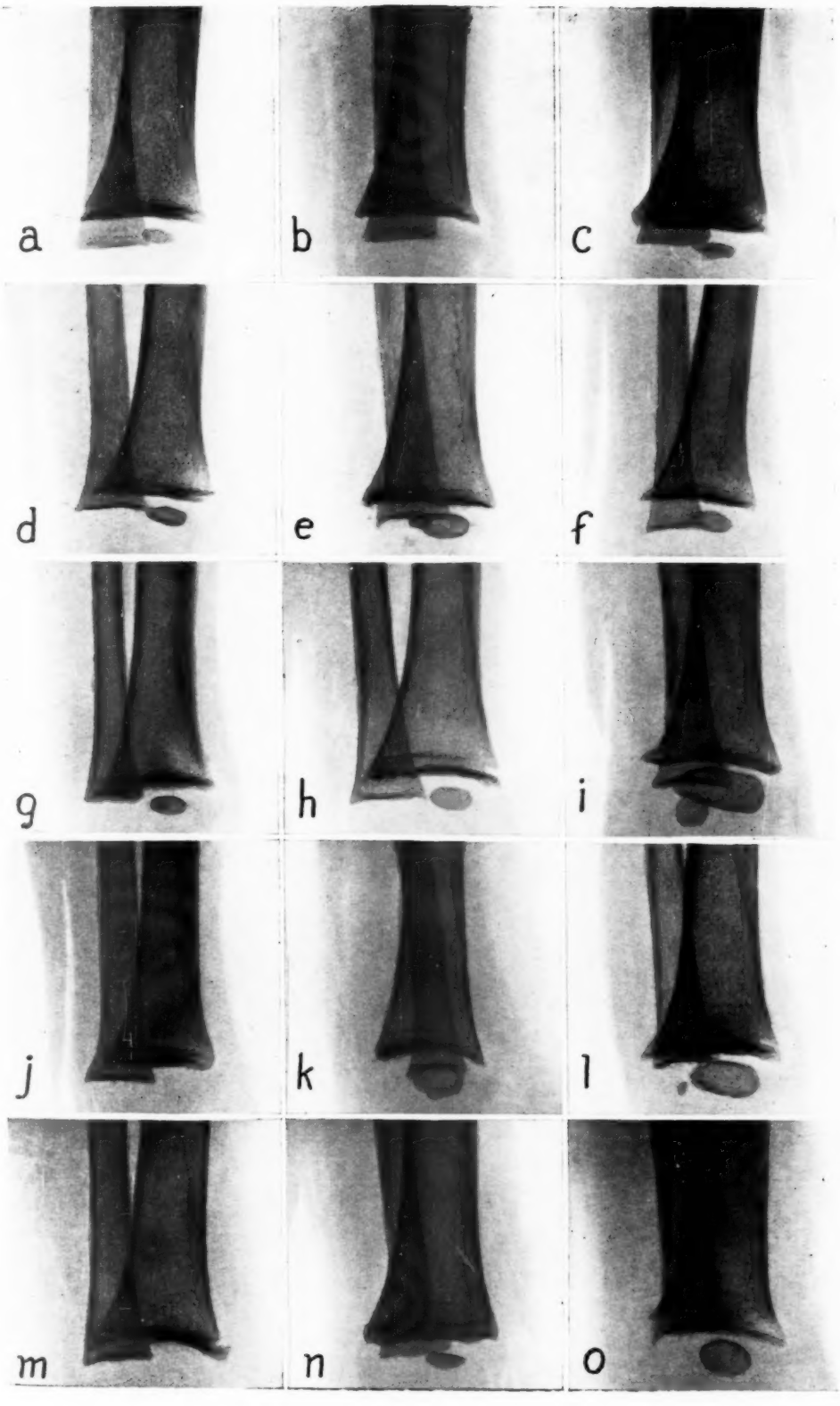

FIG. 2.—For explanation see text.

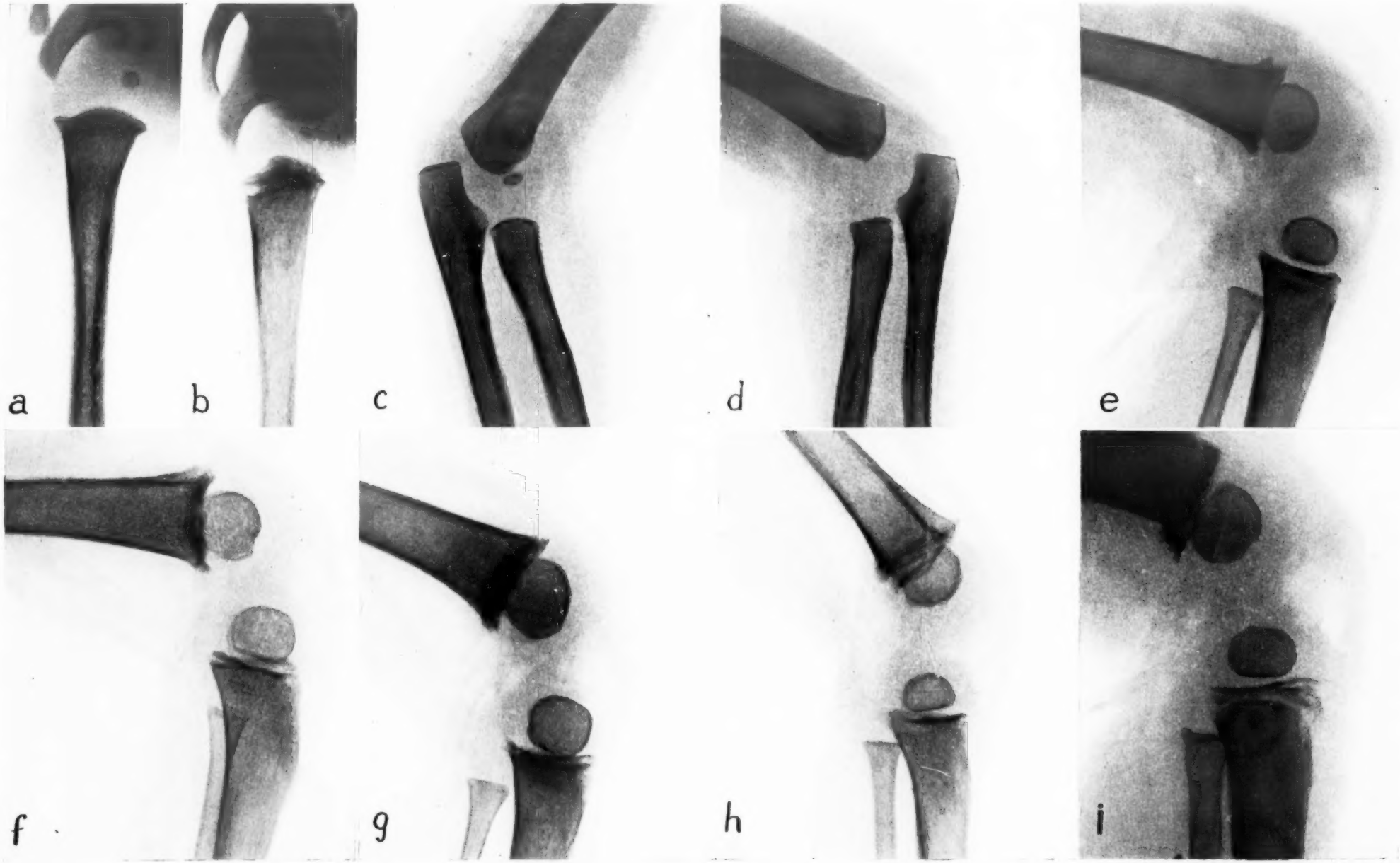

FIG. 3.—For explanation see text

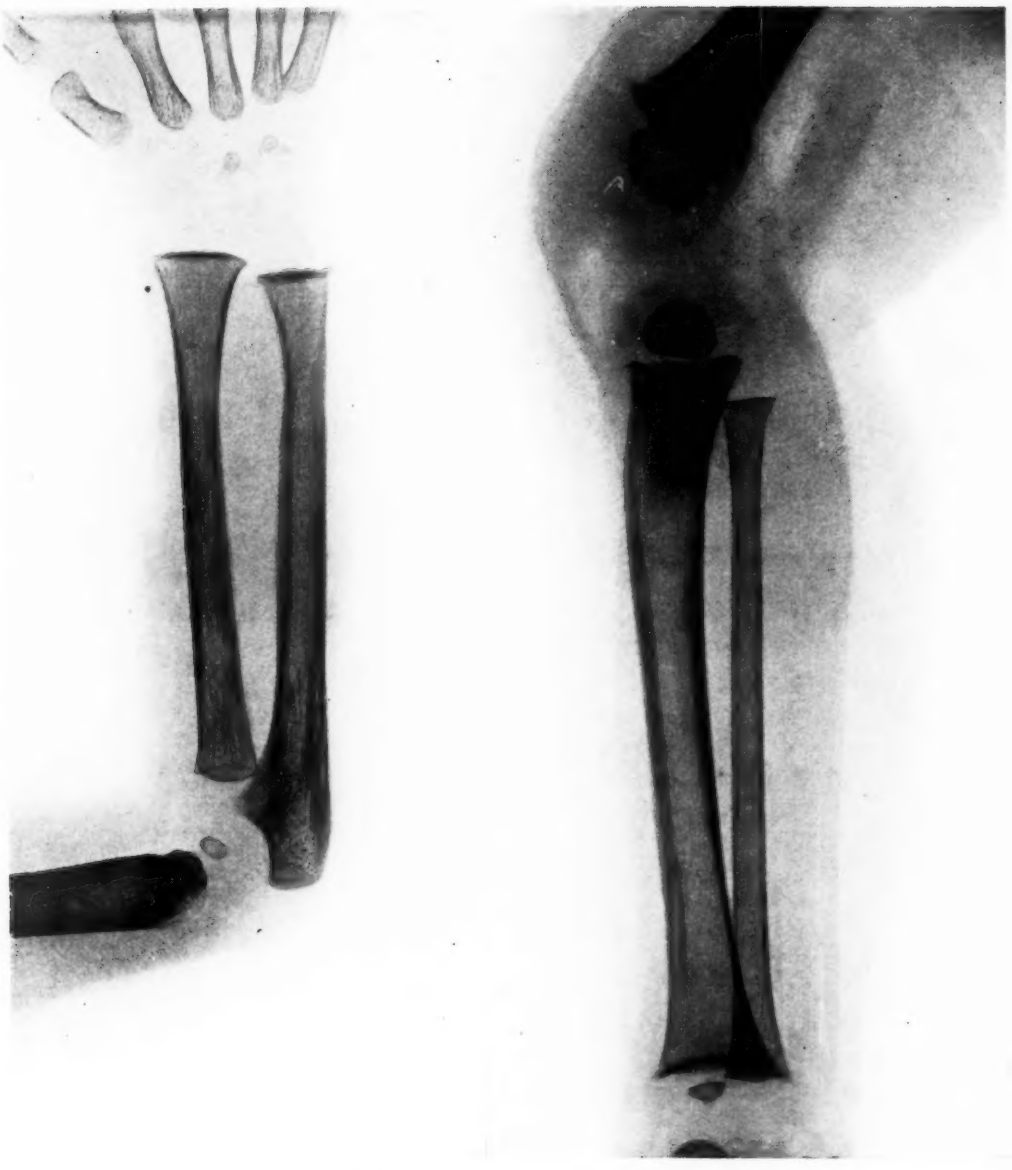

FIG. 4.—For explanation see text.

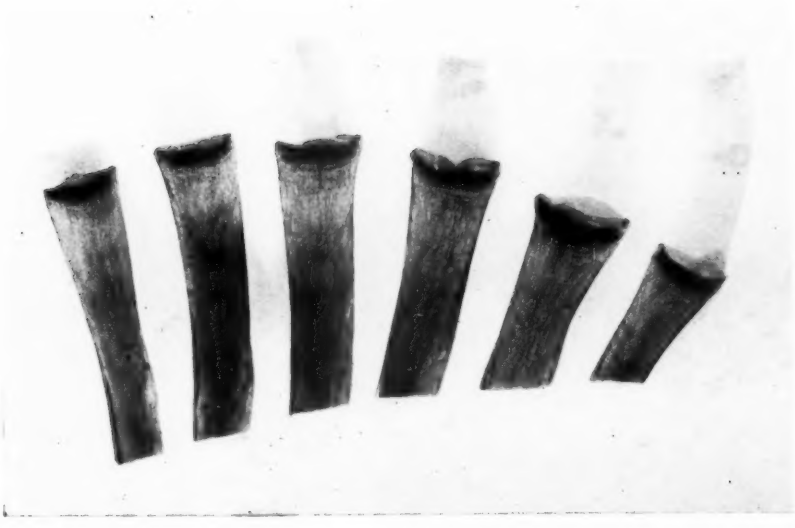

FIG. 5.—A.S., 559. X-ray picture of a series of ribs. The ribs show extreme rarefaction. The dense shadows at the ends are caused by the scorbutic lattice.

FIG. 6.—A.S., 559. Microphotograph of one of the ribs in fig. 5. The cartilage can be seen above stained deep blue. At the bottom of the cartilage the scorbutic lattice shows beautifully as a hedge of deep blue-staining trabeculae of calcified matrix substance without any addition of bone. The trabeculae of bone are greatly rarefied and are greatly reduced in number and the cortices appear as thin shells. At the lower left hand corner a round haemorrhage can be seen. The cortex and the trabeculae of bone stain pink in contrast to the lattice which stands deep blue. The preparation gives a beautiful demonstration of the differentiation of calcified matrix substance from bone by staining methods. All across the lower part of the lattice one sees fractures. Some of the trabeculae of bone are fractured also.

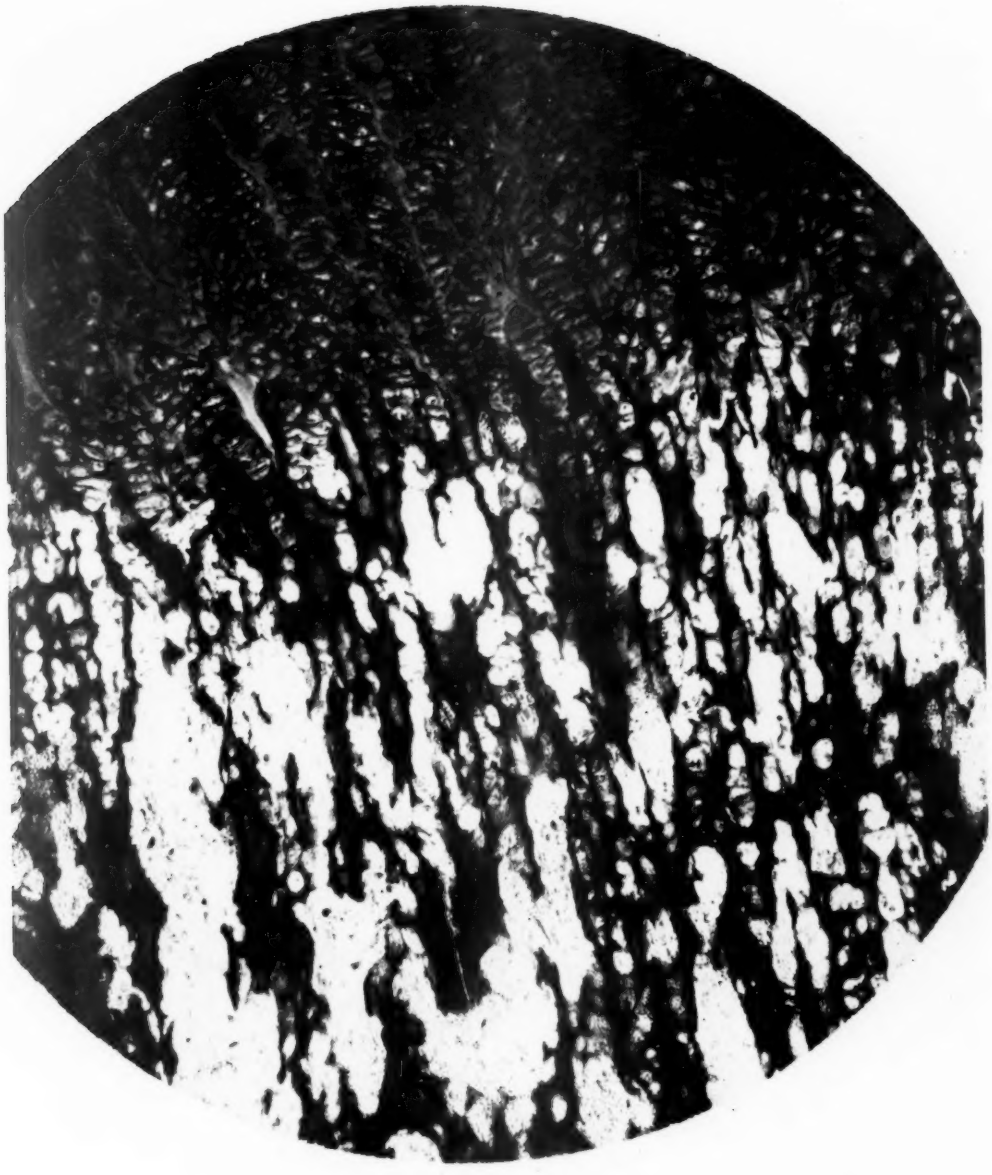

FIG. 7.—A.S., 559. Microphotograph (higher power view) of scorbutic lattice of fig. 6. Above is the proliferative cartilage. The lattice stains a deep blue and is quite devoid of any covering of bone. Bone, if present, would appear pink (grey in photograph) and would have a cellular structure. The interstices of the attice are occupied by connective tissues.

FIG. 8.—A.S. 559. Microphotograph (higher power view) of the scorbutic lattice of fig. 6. The fractures of the lattice are beautifuliy shown. One can see that the line of fracture has occurred at the junction of the lattice with the trabecular system of the shaft, because below the fracture one can identify trabeculae of bone by their cellular structure whereas above the line of fracture the dark staining lattice shows no cells. Along the line of fracture are bands of fibrin. Below is the typical connective tissue framework of the marrow.

FIG. 9.—G. H., 449. X-ray picture of a series of ribs, which show the great cupping so characteristic in the rib in advanced scurvy. The dark shadows at the sides of the cup are produced by the scorbutic lattice. Below the lattice shadows in the three ribs on the right the zones of rarefaction can be beautifully seen. The microscopic preparation, shown in fig. 10, was taken from the third rib from the right. Rickets as well as scurvy was present in this case.

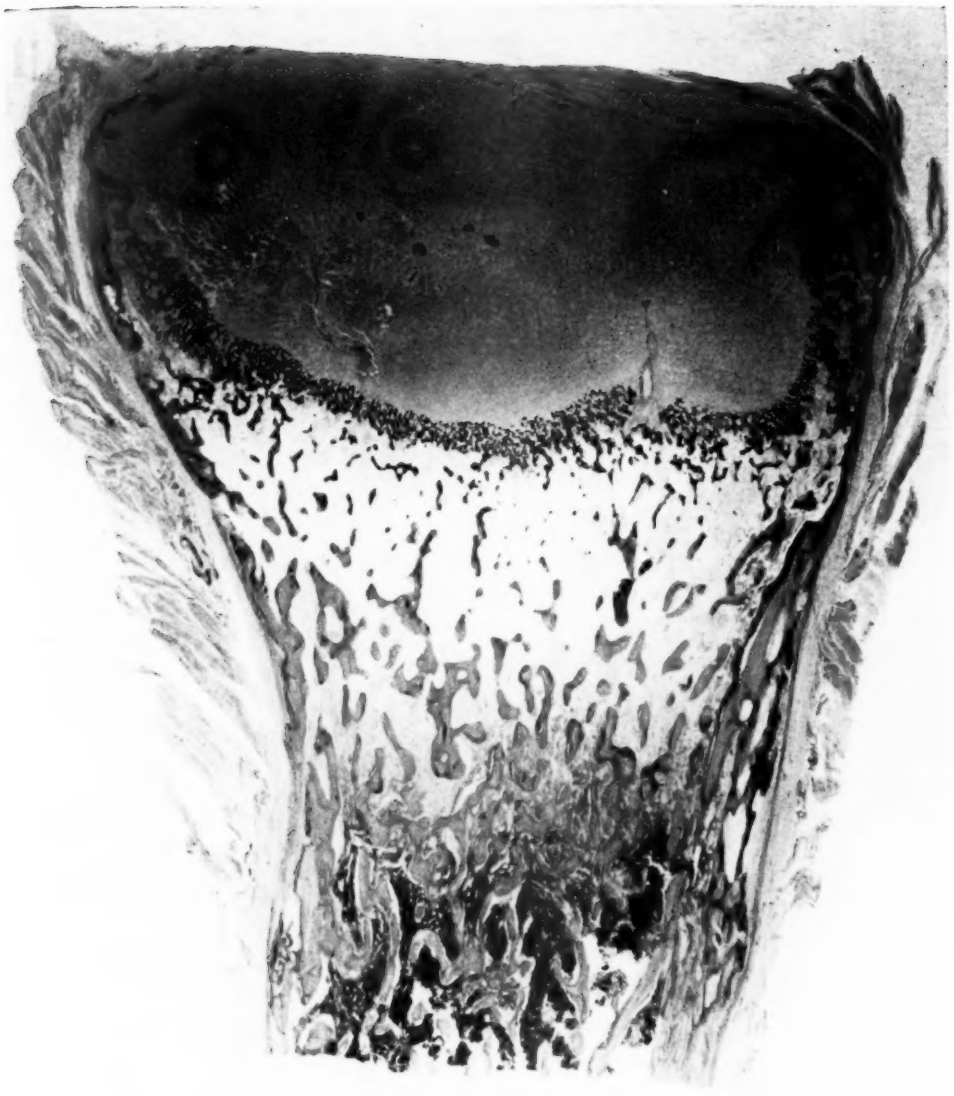

FIG. 10.—G.H. 449. Microphotograph taken from fig. 9, third rib from right. Above is the cartilage. Next below is the scorbutic lattice which stains black and has a dense structure. Below the lattice is the zone of rarefaction. In this zone the trabeculae are sparse and extremely thin. The marrow cells have gone, leaving the connective tissue framework, which appears white, exposed to view. Still lower down the trabeculae of bone, which appear pink (grey in the photograph) look fairly normal. In the lower corner of the preparation the marrow cells are present and their situation can be identified by their dark blue stain. The cortices are extremely thin and at the upper boundaries of the rarefaction zone are shell-like and fragmentary. Fractures have occurred through the lattice at many points as is indicated by fragments which lie cross-wise or at queer angles.

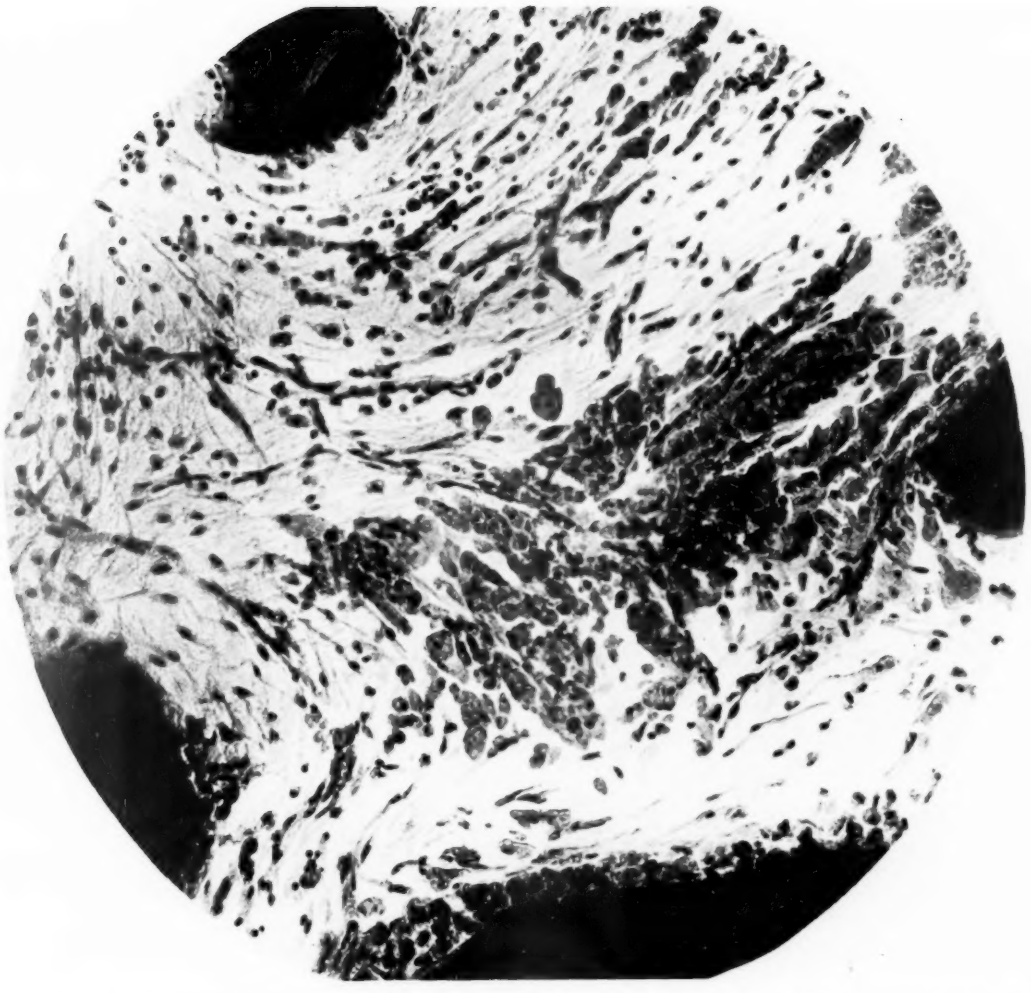

FIG. 11.—A.P., 1135. Microphotograph from the narrow cavity to show fresh haemorrhages and, also, the characteristic scorbutic changes in the marrow. The haemorrhages obviously occurred around the branches of the small vessels, which can be indistinctly seen in the microphotograph. The red blood cells were ensheathed around the branches. The marrow cells have largely gone but not entirely, as sprinklings can be seen scattered about in the connective tissue. The presence of the loose embryonic-like connective tissue between the trabeculae instead of the ordinary obscuring masses of marrow cells is characteristic of scurvy histologically.

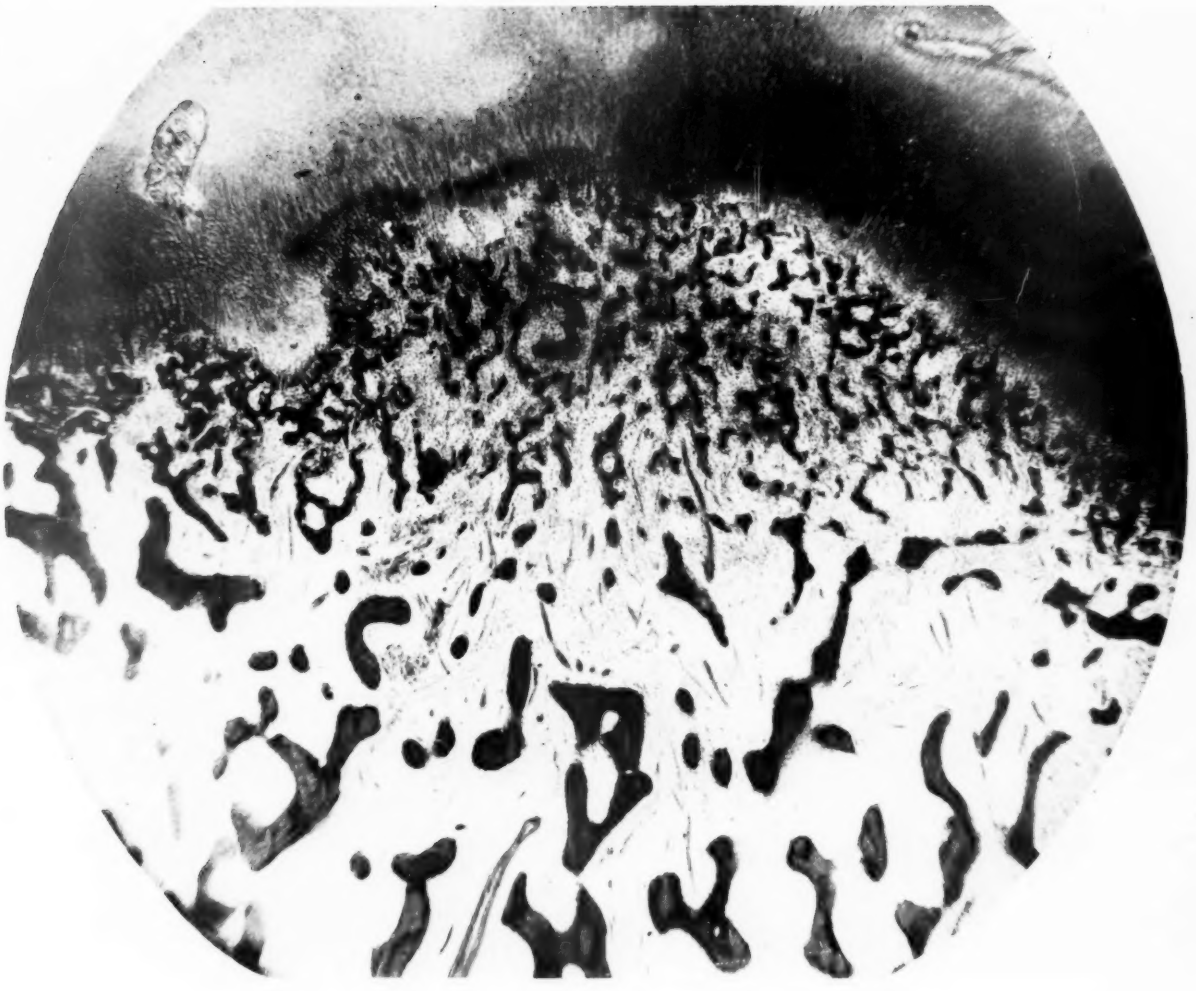

FIG. 12.—A.P., 1135. Microphotograph from the upper end of the humerus showing comminution of the lattice. At the top of the microphotograph is the cartilage, immediately below is the lattice which has been reduced to fragments. At the bottom one sees bone, the cells of which are not visible, because out of focus. Everywhere between the trabeculae is the typical scorbutic connective tissue.

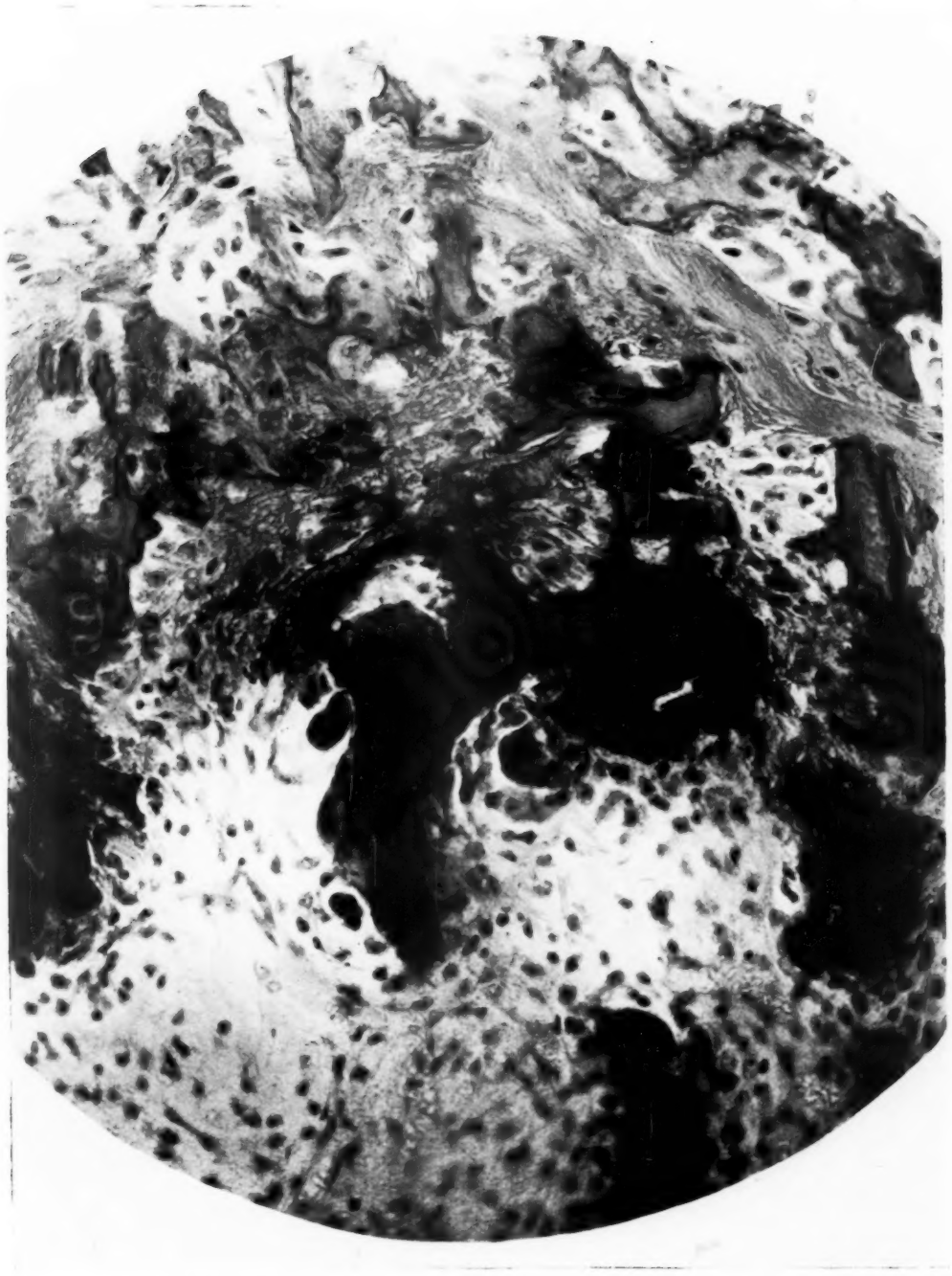

FIG. 13.—M.B. 24.—Microphotograph (high power view) of rib shown in fig. 36, in order to illustrate fracture of the lattice. The fractures and the masses of fibrin which run between the fragments can be beautifully seen The two large black fragments in the centre of the picture have been impacted and are disintegrating in their interiors. Around the fragments one sees many connective tissue-like cells which are osteoblasts. Large osteoclasts can also be seen. The marrow cells are gone.

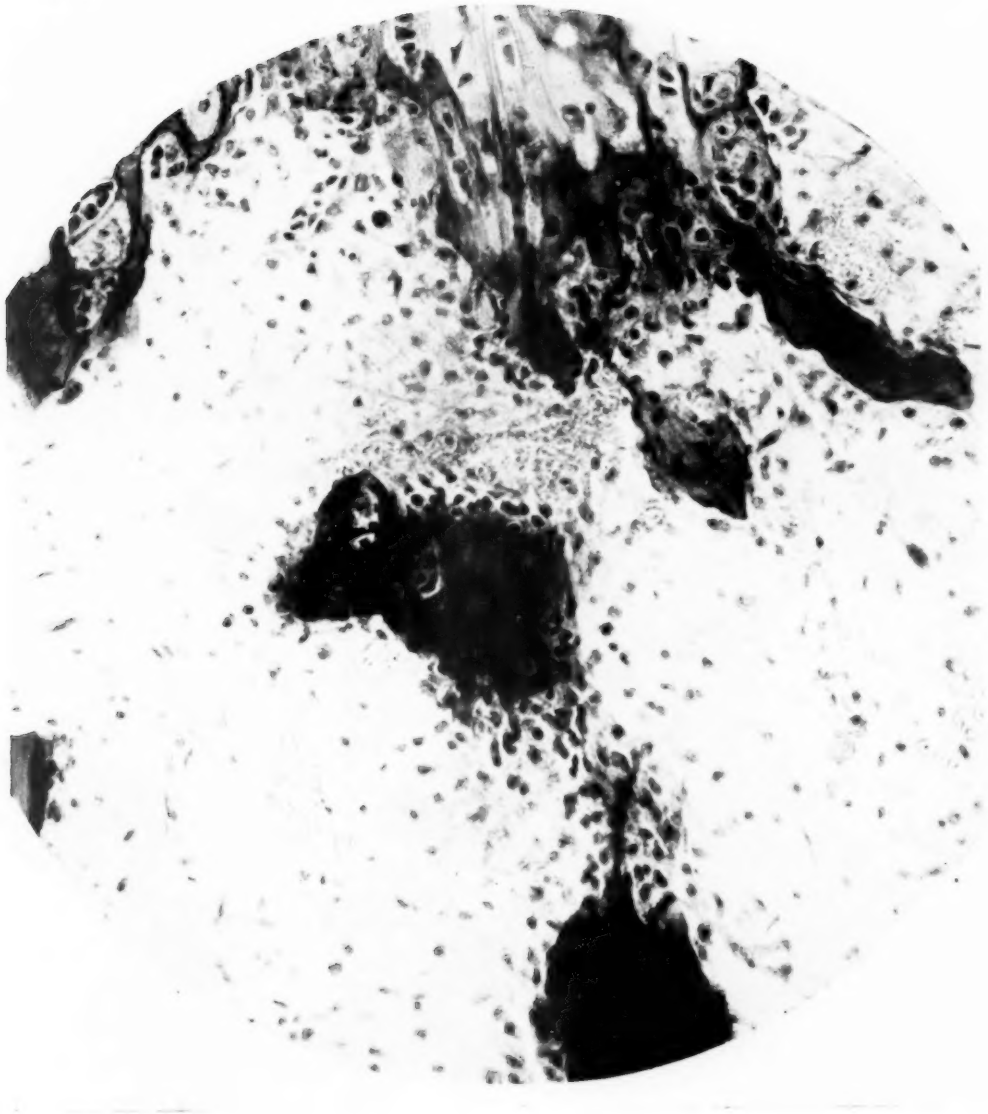

Fig. 14.—M. B., 24. Microphotograph from rib of fig. 36 showing the large numbers of osteoblasts which surround the fractured fragments of lattice. In the text it was stated that the osteoblasts surrounded them, like 'swarms of bees'. The fragments lie in typical scorbutic connective tissue, the 'Gerüstmark' of the Germans.

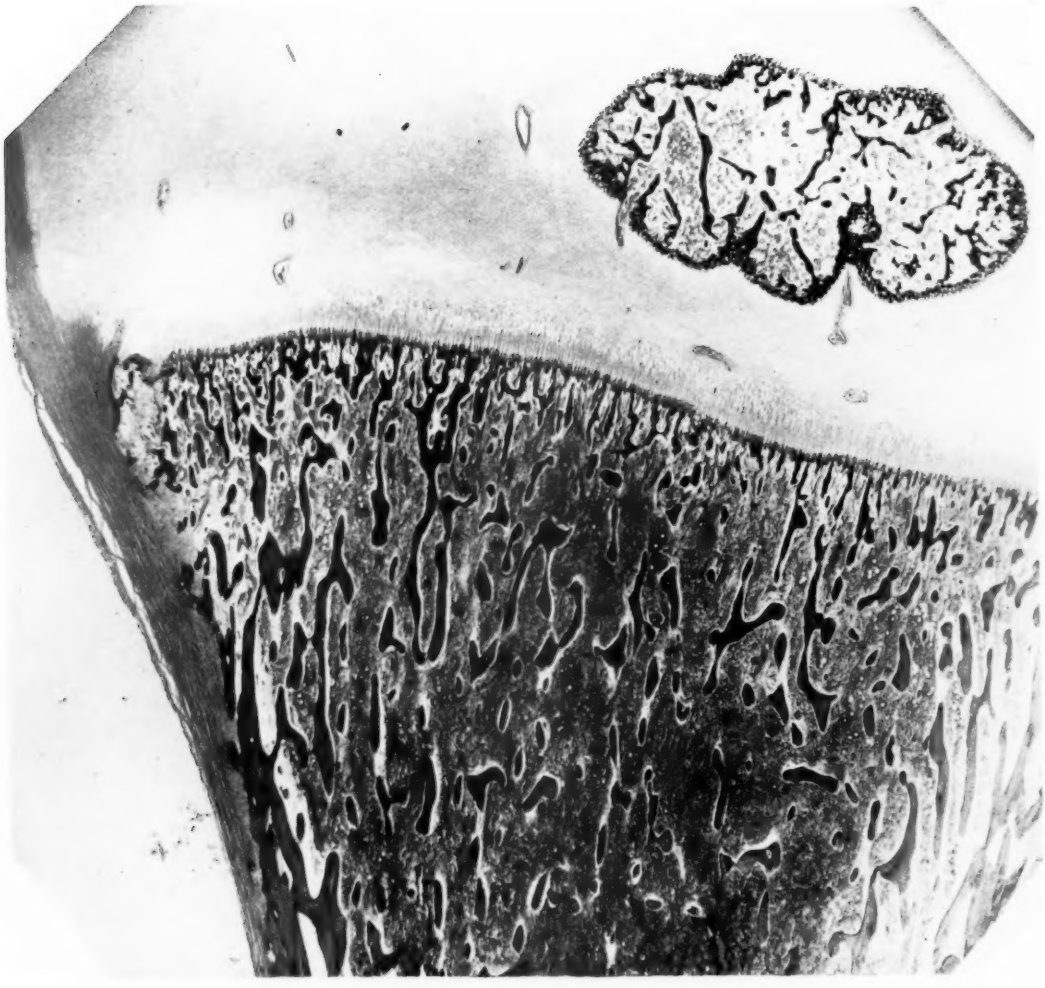

FIG. 15.—M.B., 24. Microphotograph from the lower end of the tibia, showing a beautiful 'corner' lesion of rarefaction. The cortex has been absorbed in large part; only fragments remain. The adjacent trabecular framework has also been largely absorbed. The scorbutic lesions seem to be limited to the corner. In reality, however, minute fractures of the finer structure were found with the microscope in the underparts of the lattice at a number of points.

Fig. 16.—M. B., 24. Microphotograph (higher power view) of corner shown in fig. 15. The trabeculae have disappeared from the central area but their debris can still be identified by the groups of osteoblasts which surround them. The cortical shell on the left is undergoing destruction. The soft parts show no sign of injury. It is obvious, however, that the trabeculae and cortex are disintegrating and disappearing.

FIG. 17.—M. B., 24. X-ray picture of the lower ends of the radius and ulna. The histological preparations in the microphotographs in figs. 18 and 19 were taken from the radius. There is a minute spot of rarefaction at the outer corner of the radius which is too small to show clearly in the x-ray film. The outer corner in the film has merely an indistinct outline.

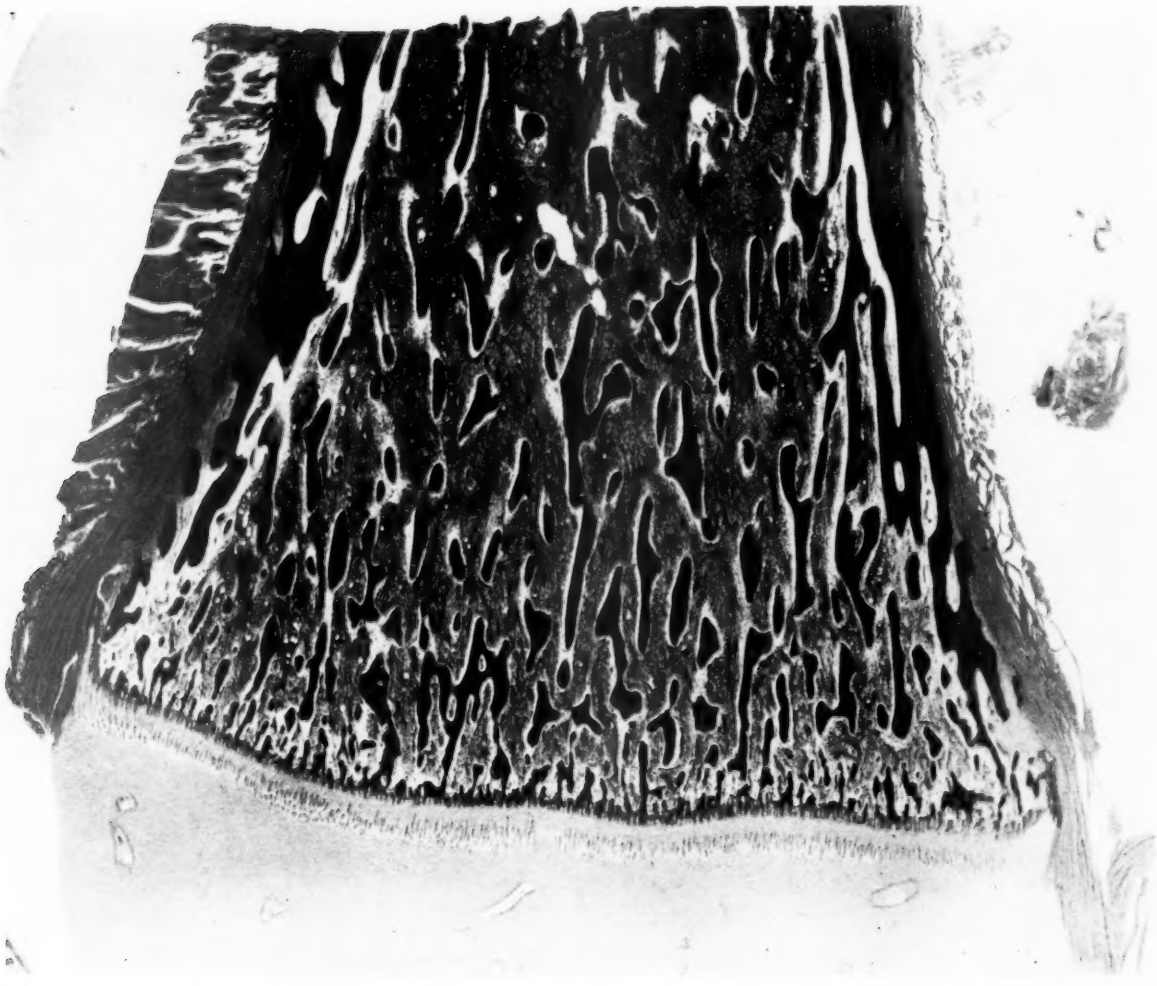

FIG. 18.—M. B., 24. Microphotograph from radius in fig. 17. The low power microphotograph shows quite beautifully the spot of rarefaction at the outer corner of the radius on the left-hand side. The cortex has been partially absorbed as have, also, some of the adjacent trabeculae. A similar area of scorbutic rarefaction can be seen in the opposite corner. At scattered points in the under surface of the lattice fractures were found which were too small to show in this view.

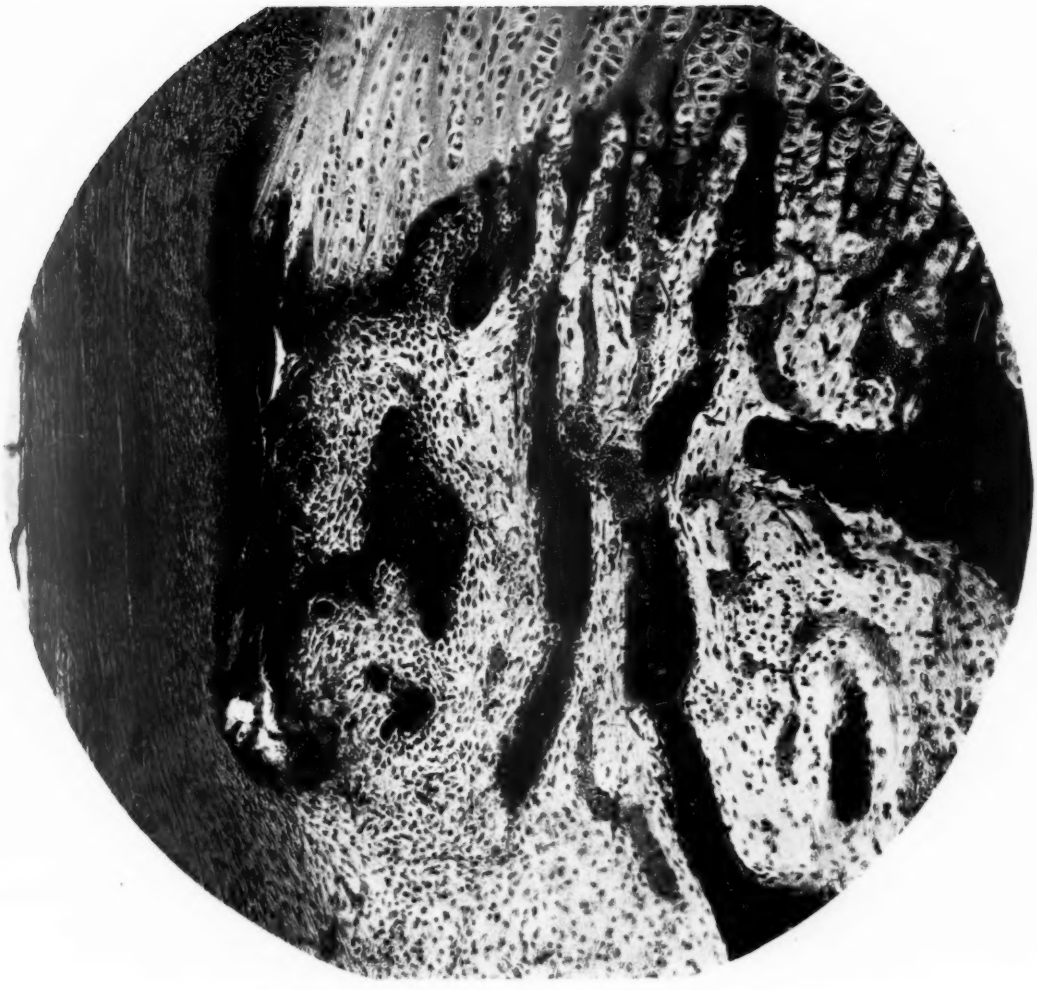

FIG. 19.—M. B., 24. A high power microphotograph showing the outer corner of the radius exhibited in fig. 17 and 18. The cortex is disintegrating and has disappeared entirely in the lower part of this view. The fragment which is shown is filled with osteoclasts and shows a cystic formation below. Crowds of osteoblasts surround one of the adjacent trabeculae, which is undergoing destruction.

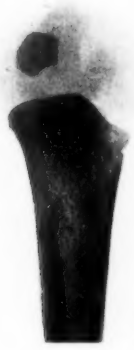

FIG. 20.—M. B., 24. X-ray picture of the upper end of the humerus. A glance shows the spot of rarefaction in the characteristic situation at the outer angle.

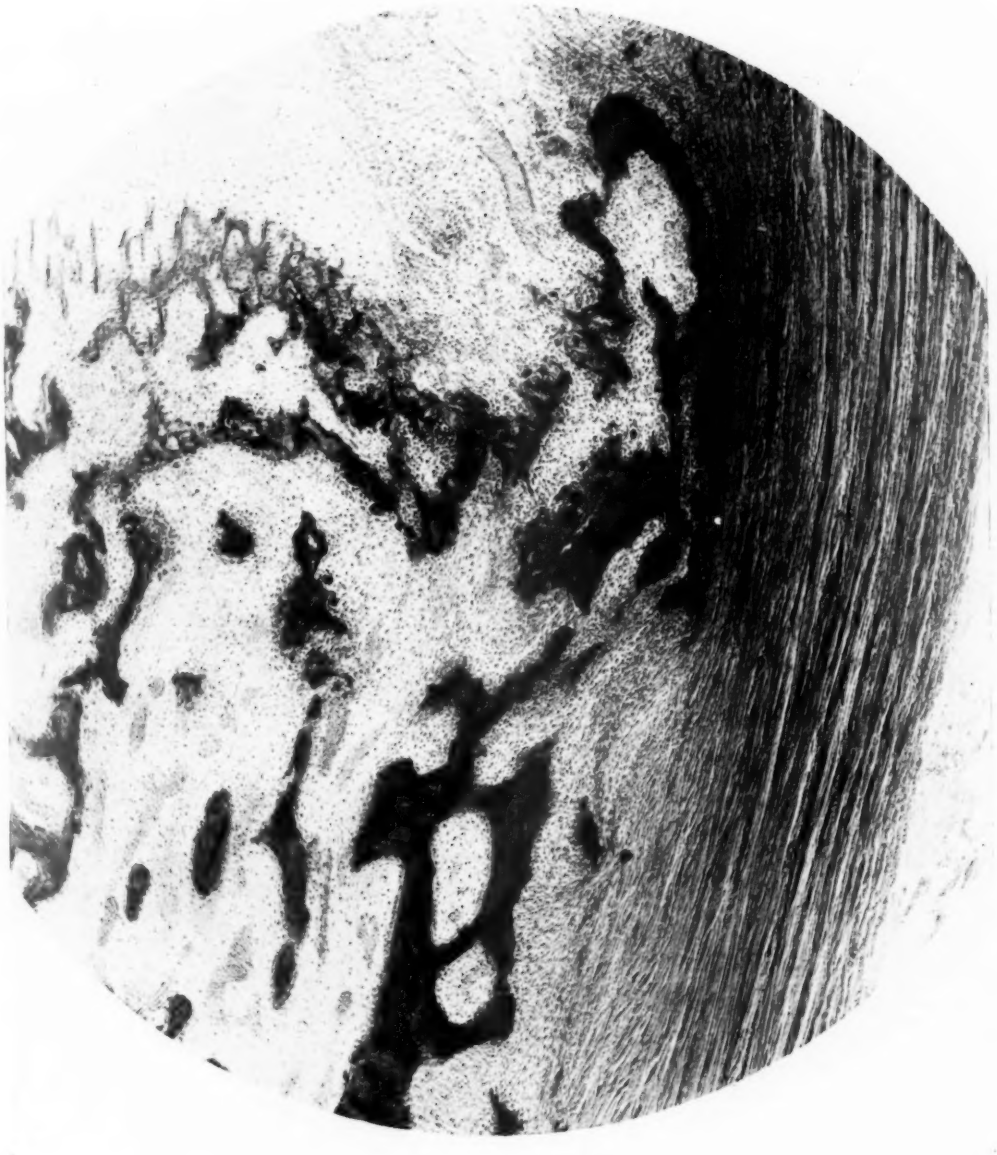

FIG. 21.—M. B., 24. Microphotograph from the outer angle of the upper end of the humerus shown in fig. 20. It can at once be seen that the corner is most abnormal. The cortex is largely gone and that which remains has been fractured and is being destroyed. The adjacent parts of the lattice have also been fractured and are being removed. Swarms of osteoblasts surround the fragments. It is interesting to see that bone tissue has formed considerably to the outer side and above the proliferative cartilage.

FIG. 22.—M. B., 24. X-ray picture of lower end of femur. The inner corner, left in the figure, shows a characteristic spot of rarefaction.

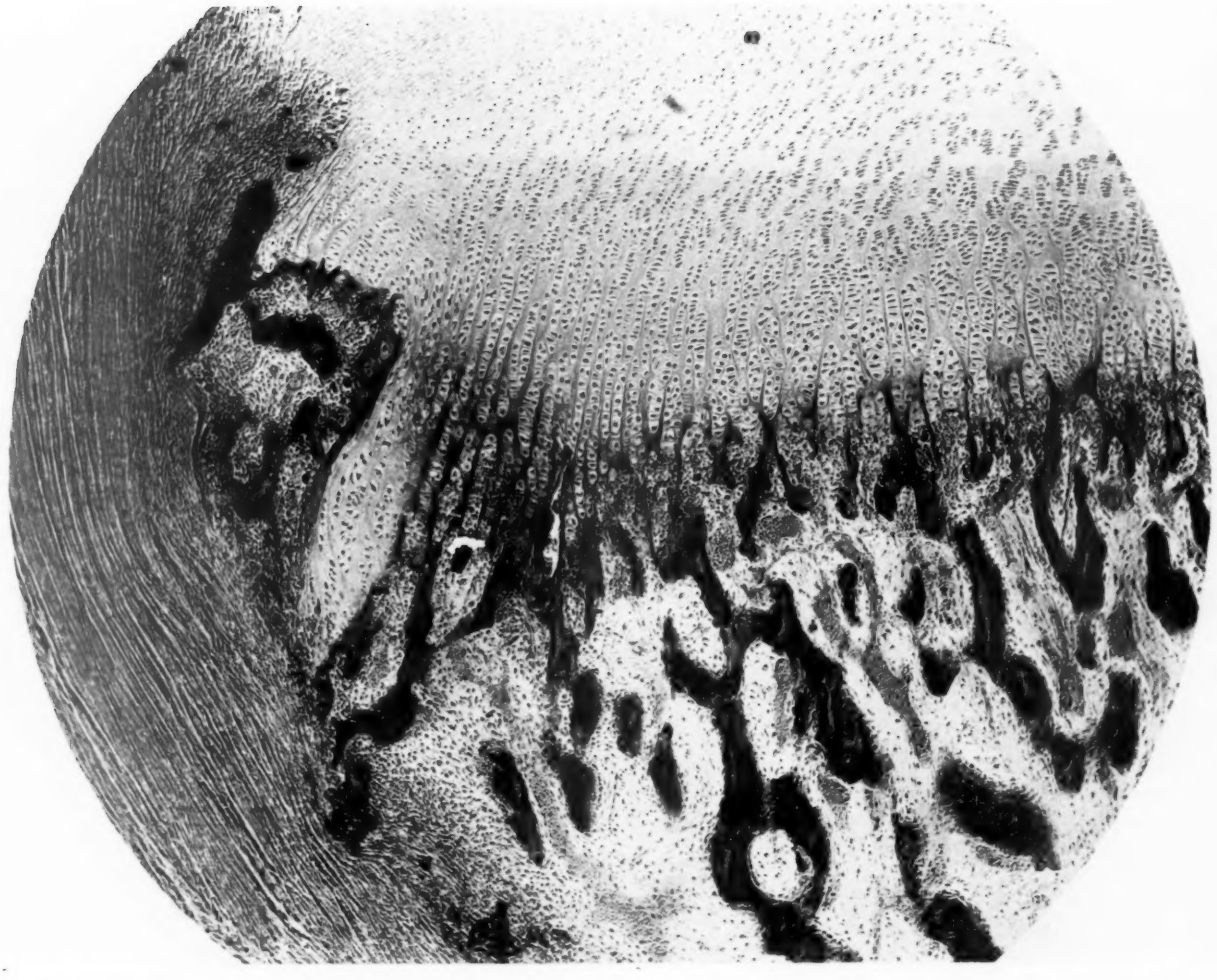

FIG. 23.—M. B., 24. Microphotograph of inner corner of lower end of femur from fig. 22, showing extensive destruction of the cortex and adjacent lattice. A lattice has started to form at the side of the proliferative cartilage, separated from the rest by a tongue of the latter which extends downwards almost to the periosteum. Rarefaction is rampant in this island of lattice separated by the tongue. If this island of lattice were only larger, it might give rise in the x-ray picture to the appearance of ' over-extension and pointing ' of the corner of the end of the shaft.

FIG. 24.—A. P., 1135. X-ray picture of the lower ends of the tibia and fibula, showing lattice formation, cupping and also ' bagging ' of the outer corner (right in figure).

FIG. 25.—A. P., 1135. Microphotograph of the outer corner of the lower end of the tibia exhibited in fig 24. The microphotograph gives a good example of ' bagging ' and also a most typical scorbutic affection of the bone. The cortex has disappeared except for scattered fragments. Extensive fractures of the lattice have taken place. As the result of the loss of cortical support the ' corner " soft tissues have been squeezed outwards. The periosteum remains and forms the outer boundary of the ' bag.' This microphotograph makes clear why the bagged area should appear so rarefied in the x-ray film and devoid of cortical shadow, and why it should extend out beyond and envelope the end of the lattice.

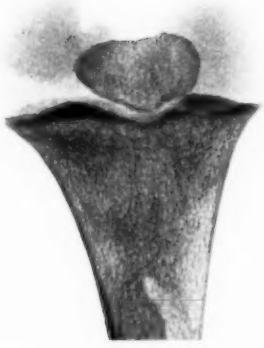

FIG. 26.—A. P., 1135. X-ray picture of the lower end of the femur, showing a scorbutic lattice, zone of rarefaction, 'bagging,' over-extension, and pointing at both corners.

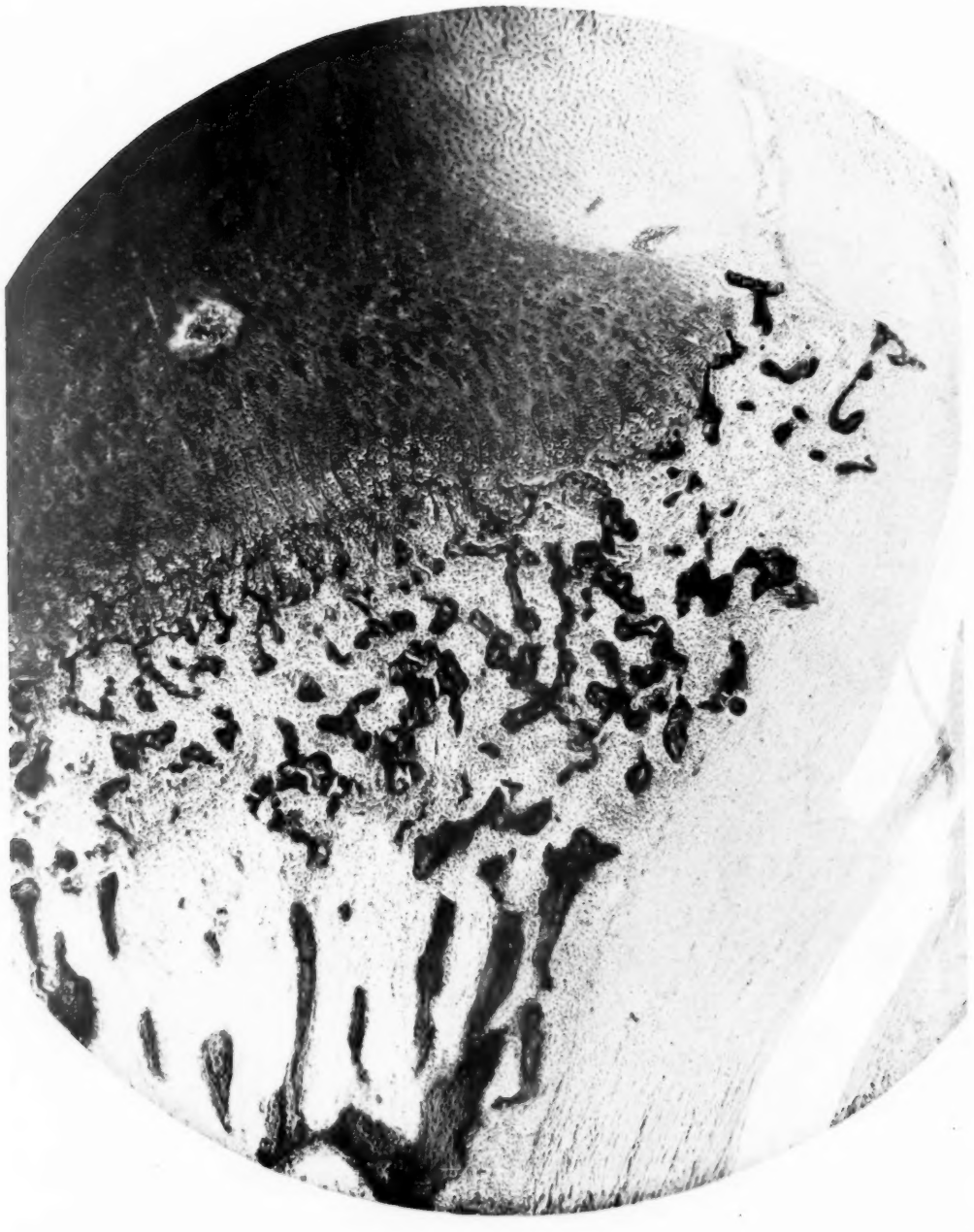

FIG. 27.—A. P., 1135. Microphotograph of the outer corner (right in fig.) of the lower end of femur (fig. 26). This microphotograph really needs no explanation. The lattice has been completely shattered, the cortex has gone. Fragments of the lattice extend to the extreme limit of the proliferative cartilage and considerably to the outer side of the latter.

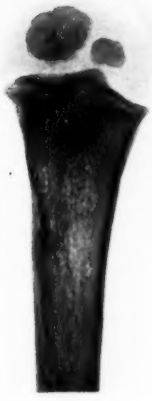

FIG. 28.—A. P., 1135. X-ray picture of the upper end of the humerus. The outer corner shows a minute spot of rarefaction.

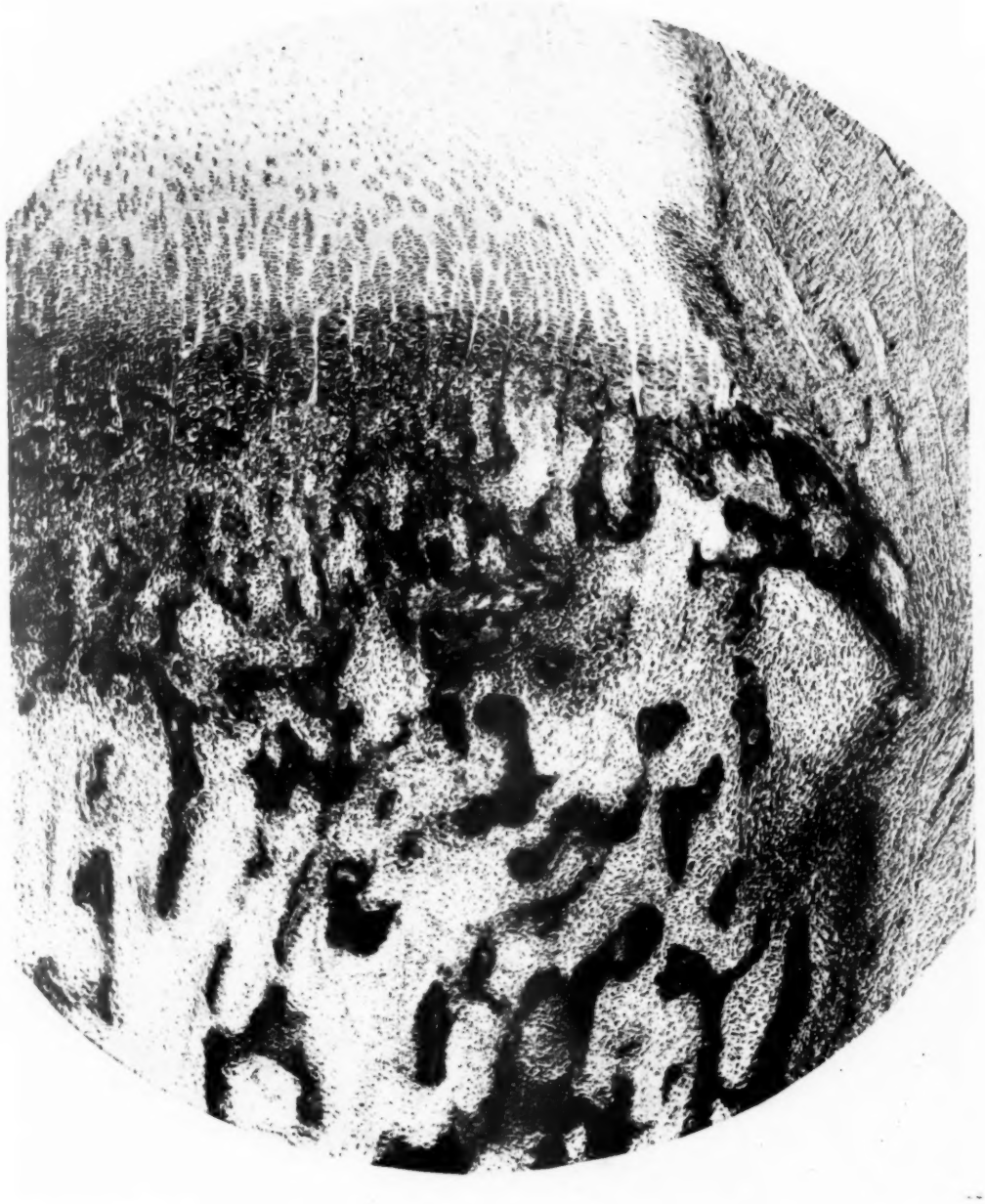

FIG. 29.—A. P., 1135. Microphotograph of outer corner of upper end of humerus as shown in fig. 28, showing a characteristic scorbutic lesion. The heavy lattice has been shattered and masses of osteoblasts surround the fragments. The cortex has been partially destroyed and areas of rarefaction are developing in the interior.

FIG. 30.—A. P., 1135. X-ray picture of upper end of tibia and fibula. The inner corner of the tibia has been injured at autopsy. The outer corner shows a minute spot of rarefaction.

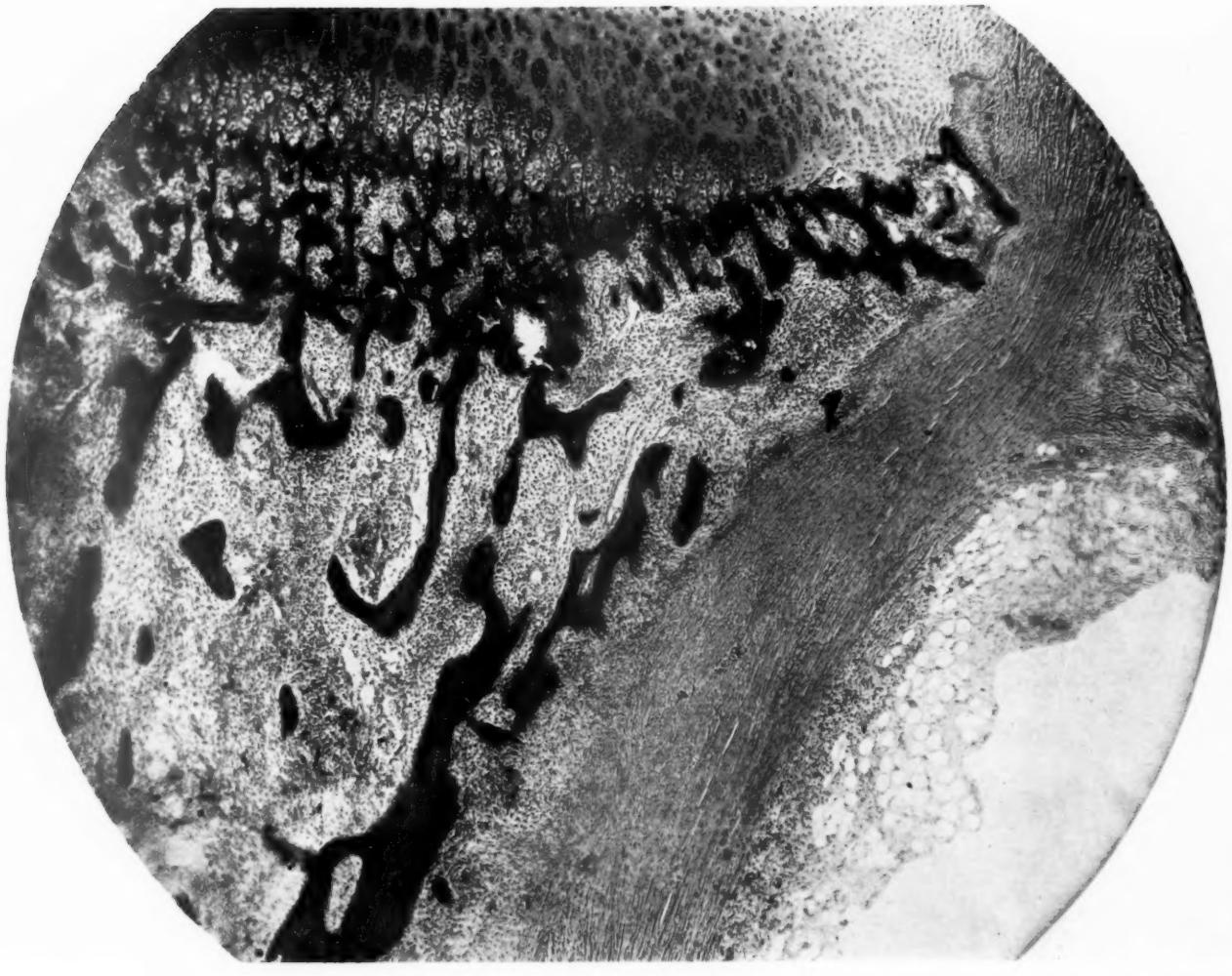

FIG. 31.—A. P., 1135. Microphotograph of outer corner of upper end of tibia, as shown in fig. 30. The microphotograph illustrates beautifully the fractures of the lattice with a splinter lying at right angles, also loss of cortex beneath the lattice just at the corner. The loss of the cortex just under the outer end of the lattice might give rise to the appearance in the x-ray film of 'over-extension' of the corner and 'pointing.' Extensive rarefaction has taken place in the framework of bone.

FIG. 32.—A. P., 1135. X-ray picture of the upper end of the ulna. This fails to give any indication of scurvy. Nevertheless, the histological preparation from the posterior angle of the upper end of the olecranon shows a scorbutic lesion.

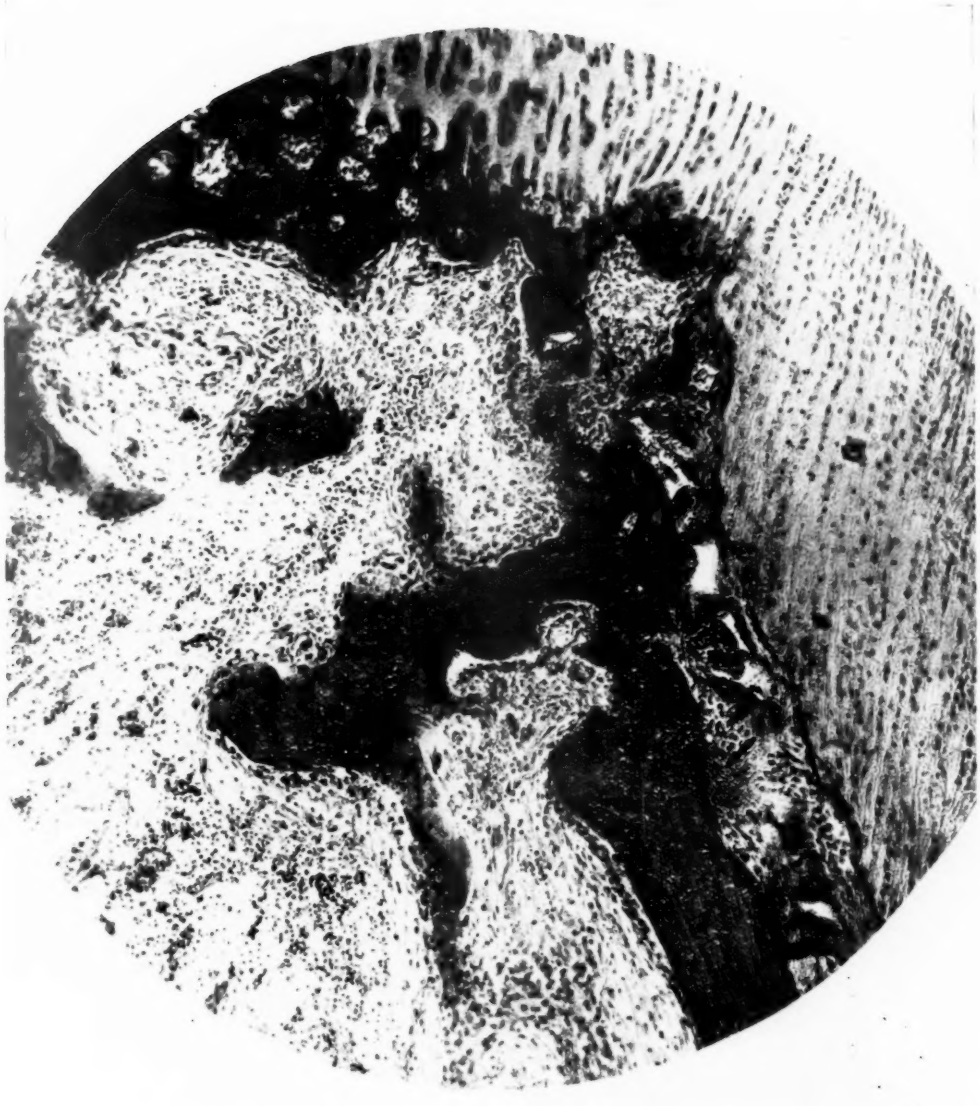

FIG. 33.—A. P., 1135. Microphotograph of posterior corner of upper end of the olecranon as shown in fig. 32. Fractures of the lattice have occurred, presumably from pressure of the elbow against the bed. The fragments are in process of absorption. The contrast between the bone with its cells and the lattice substance without cells and coloured deep blue is striking.

FIG. 35.—A. B., 1182. This is the only example of true 'bayonet deformity' encountered. The drawing has been taken from the ninth rib. This rib and the tenth alone showed the bayonet deformity. The ribs above showed the ordinary scorbutic deformity. The rib has been cut transversely so that the upper contour corresponds to the outer surface of the costo-chondral junction. Examination of the drawing shows that the resting cartilage has been pulled inwards on the proliferative cartilage, so that the outer part of the latter overlaps the former and sticks out above it forming a ledge. The examining finger passing along the outer surface of such a rib, would encounter a ledge and drop down on the cartilage. But the ledge is formed not by the end of the bone but by the proliferative cartilage. The bayonet deformity is most uncommon in rickets and is almost a misnomer. In this case advanced rickets was present. It is suspected that the bayonet deformity is always a combination of scurvy and rickets and occurs only in the lower true ribs and is caused by the pull of the diaphragm which is attached to the resting cartilage.

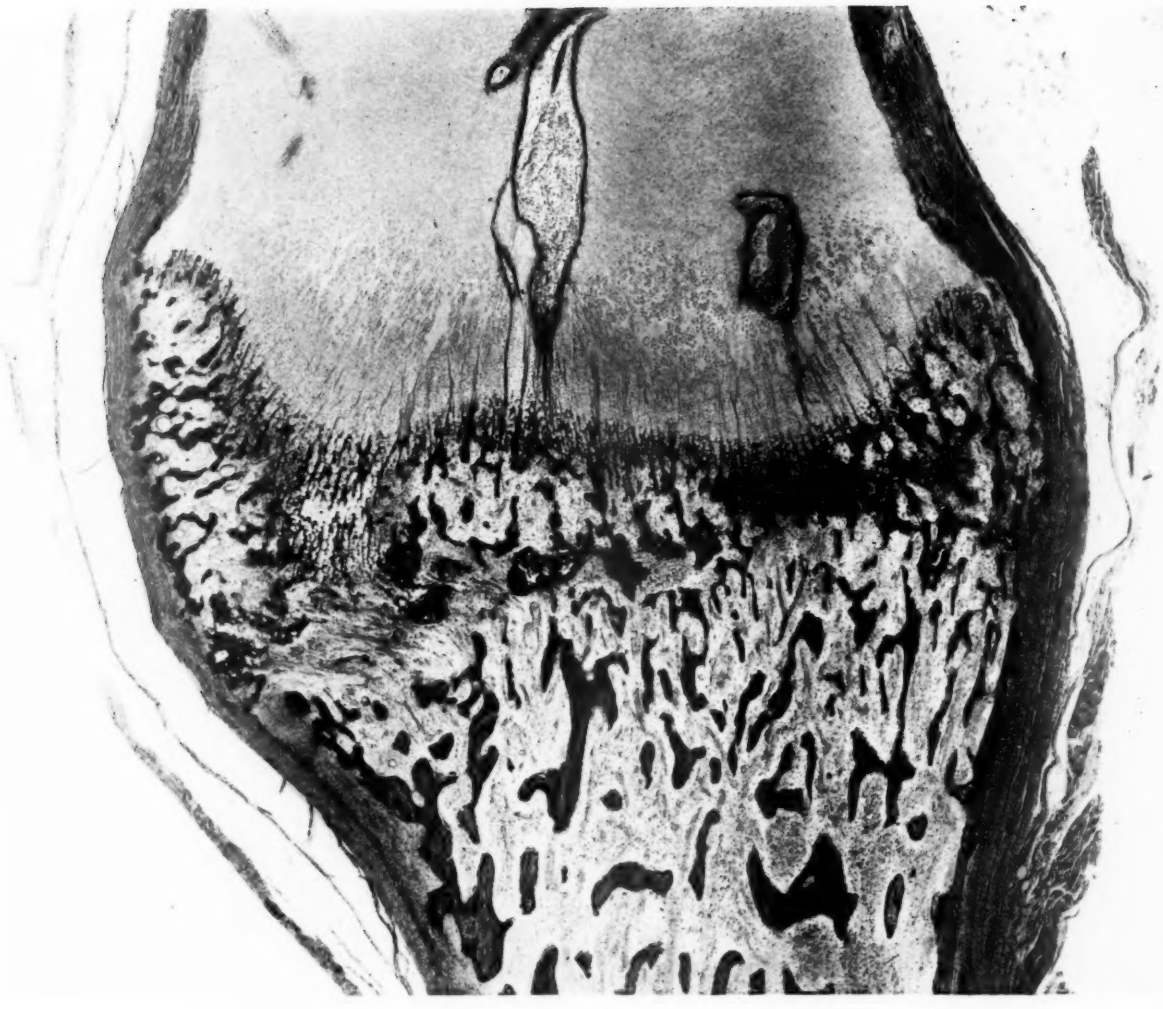

FIG. 36.—M. B., 24. Microphotograph of a rib, cut in a transverse direction to show the shift inwards of the cartilage on the shaft. The outer border of the costo-chondral junction is to the right. It is seen at once that a fracture has taken place through the under surface of the lattice and extends entirely across the bone. The lattice fragments have been impacted in some places and in others have been entirely absorbed. Through this study of the finer structure, in particular the blood vessels and strands of fibrin and the fragments of trabeculae one can be certain that the cartilage with its attached lattice has shifted slightly in an inwards direction on the broken end of the shaft. One can also be certain that the cartilage has been bent inwards slightly on the shaft so that the angle formed by the two is slightly greater than normal. On the left-hand side in the line of fracture is seen an area of rarefaction. Above this area is unbroken lattice. From this sample of unbroken lattice it could be imagined what would be the appearance of the lattice if fracture had never occurred. The development of the shaft around the sides of the proliferative cartilage is beautifully shown.

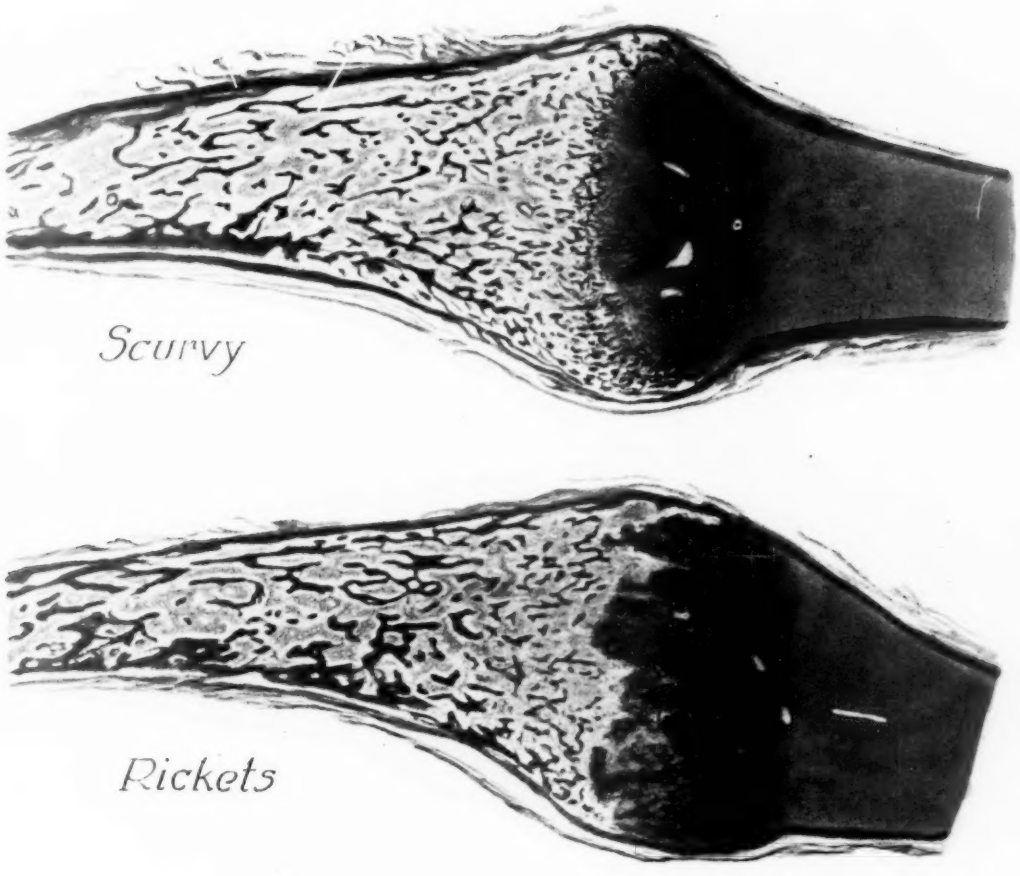

FIG. 37.—Camera lucida drawing of transverse sections of a typical scorbutic and a rachitic rib. The upper borders correspond to the outer surfaces of the costo-chondral junctions. The drawings speak for themselves. In rickets the sharp angle of junction between cartilage and shaft is not apt to be present because of the deep rachitic intermediate zone interposed between the proliferative cartilage and the shaft.

VITAMIN C AND ITS EFFECTS ON THE STRUCTURE OF THE TEETH

BY

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Since scurvy, whether occurring in adults or infants has been recognized, the effect of this disease on the gums has been familiar. The sequence of events, swelling, bleeding from the gums and progressive loosening of the teeth, is well known. It is interesting to note that in infantile scurvy these changes only occur when teeth are present or just on the point of eruption. In their early experimental research into the action of vitamin C, Holst and Frölich[9] in 1912 noted in guinea-pigs the occurrence of swelling of the gums and loosening of the teeth, but the first observation on the effect of vitamin C deficiency on actual tooth structure seems to have been that of Jackson and Moore[11] in 1916, who noted the presence of haemorrhages in the pulps of the teeth in guinea-pigs. This was the first account of the effect of vitamin C deficiency on tooth structure as opposed to the supporting structures, such as alveolar bone, periodontal membrane and gum.

The next stage was the work of Zilva and Wells[18] who showed that changes occur in the pulps of the teeth in guinea-pigs when deprived of vitamin C. Not only haemorrhages occur but a series of changes in the cellular structure are found which lead eventually to a disintegration of the cells and their replacement by fibrous tissue. Zilva and Wells described the changes as being in the nature of a fibrous degeneration. They found that the mildest degree of scurvy which could be recognized at post-mortem examination produced changes in the teeth of guinea-pigs. In more advanced degrees of scurvy the odontoblast layer of cells became disorganized until, eventually, all traces of cellular organization were lost and replaced by fibrous tissue. The fine fibrillar connective tissue which normally forms a supporting network in the dental pulp, either became grossly hypertrophied or else replaced by a new form of fibrous tissue devoid of cells. The dentine was irregular and osteoid. In view of the fact that the teeth are the first structures to be affected in experimental scurvy, Zilva and Wells made the interesting suggestion that transient conditions of infantile scurvy may occur more frequently than had been supposed and that it is not unreasonable to assume that the teeth may be affected in this way.

Following the work of Zilva and Wells came the investigations of P. R. Howe[10], alone or in conjunction with other workers, from 1920 on-

wards. In 1920 Howe noted that a scorbutic diet made the teeth of guinea-pigs become elongated, irregular and loose. He described the dental findings as simulating pyorrhoea more closely than any pathological condition of the teeth artificially produced. He found that lesions of the dental pulp occurred before grosser indications of scurvy became manifest. The actual diet given is not stated, and though it may be concluded that it was deficient in vitamin C, yet it is not known how far other vitamins were present or inadequate.

In 1923 Howe carried the picture further. When guinea-pigs were fed on a diet adequate in all respects except vitamin C, extensive decalcification of enamel and dentine occurred regularly with the formation of cavities. The teeth became loose and elongated, with pus formation. These effects could be cured by the addition of orange juice to the diet. He also found that tartar was deposited on the teeth when vitamin C was withheld and that this disappeared when orange juice was added to the food.

A closer study of the changes produced in the teeth of guinea-pigs by a diet deficient in vitamin C was made by G. Toverud[15]. She found that the orthodentine (normal tubular dentine) was replaced by osteodentine, a coarse dentine without tubules and resembling bone, which normally closes the pulp chamber towards the cutting edge as the tooth is worn away, but in far less amount in scurvy. The osteodentine, including degenerating odontoblasts, reached toward the apex of the tooth and there was only a narrow zone of normal dentine surrounding it. The pulp tissue was so degenerated that scarcely any of the normal cellular elements could be recognized, and in severe cases the only trace found was the presence of degenerated odontoblasts. Fatty degeneration was frequently present. The process of cellular disintegration began by haemorrhages in the upper part of the pulp and extended towards the base of the tooth. The degree of degeneration varied according to the length of time the animal had been on a scorbutic diet. Some chemical analyses of scorbutic teeth were given by Toverud. The results show a reduction in the amount of ash and calcium and an increase in magnesium in scorbutic teeth as compared to normal. The reduction of ash and calcium was not so marked as the histological appearances would suggest and Toverud explained this on the grounds that the pulp chamber was partly filled up with pathological calcified tissue. The reduction in ash and calcium and the increase in magnesium was greatest in those animals fed on a diet deficient in calcium as well as vitamin C. Toverud regards the substitution of calcium by magnesium as nature's attempt to maintain the amount of salts in the tooth when calcium is not available, but it is a pathological process and should be regarded as a form of osteomalacia. Toverud points out that in the guinea-pig the teeth are constantly growing and it may be that an animal with teeth of limited growth, as in man and most animals, when fed on a scorbutic diet, may be unable to form normal tooth tissue.

Perhaps the most important work on the effect of a scorbutic diet on the teeth is that of A. Höjer[6] which appeared in 1924 and at once attracted much attention. In common with other investigators, Höjer used the guinea-pig. Not only were the teeth investigated but the whole effect of scurvy was considered. The experimental animals were given a basal diet complete in all respects except that it contained no anti-scorbutics. The basal diet consisted of crushed oats, bran, and milk freed from vitamin C by being strongly aerated at 100° C. for one hour. Out of 63 animals fed exclusively on this diet, 58 showed signs of scurvy. Höjer's theory of the action of vitamin C is that its presence is necessary to enable highly-organized, quickly-growing, active cells to perform their proper tasks. When vitamin C is lacking the cells sink to a lower grade and yield a product which in quantity and quality differs from normal. This is well shown in the formative cells of the teeth which by degrees stop their activity and eventually die.

The changes in the teeth of guinea-pigs occur at an early stage of vitamin C deficiency and afford the surest clinical sign of scurvy in its latent stages. As early as eight days on a completely scorbutic diet the first changes from the normal can be seen in the teeth. The arrangement of the odontoblast cells (the cells which line the tooth pulp and are responsible for the formation of dentine) becomes altered. They lose their shape and their processes disappear. There is an amorphous calcification in the odontogenetic zone (predentine) which stains deeply. Finally, there is a complete disappearance of the odontoblasts. On the inner side of this amorphously calcified tissue a hard tissue is deposited which seems to arise from calcification of collagen fibrils. During its growth it appears to become organized into a bony but spongy and porous calcified connective tissue, called by Höjer, pulp bone. The extent of the changes depends on the course of the disease. In absolute scurvy the changes in the pulp are characterized by destruction of tissue and there is very little formation of pulp bone. The odontoblasts disappear rapidly while dilatation of the blood vessels and haemorrhages are coincident with necrosis of portions of the pulp. In some sections hollows filled with fluid were seen. Höjer noted a peculiar form of destruction of the dentine already formed at the onset of scurvy; it becomes porous through widening of the tubules so that the walls break down and adjoining tubules become confluent.

Changes in mitigated scurvy.

Animals with an anti-scorbutic dose of 0.5 c.c. of special orange juice developed latent scurvy. The sequence of changes in the teeth was slower and the tissue destruction less prominent. Isolated odontoblasts were seen which resisted changes. Many osteoblasts were present which formed pulp bone. This latter grew in strongly-branched bundles towards the centre of the pulp. Structurally, the pulp bone consisted of pulp tissue enclosed in large spaces, with small bone canals, vessels and osteoblasts. If an animal fed on a scorbutic diet was given an anti-scorbutic diet the

tooth changes were different. They were characterized by the formation of pulp bone and a new formation of odontoblasts which again became normally arranged. The reorganization of the bone of the jaw progressed concurrently with the healing changes in the teeth. Like Zilva and Wells, Höjer found that the changes in the teeth were one of the earliest signs of experimental scurvy. But he disagreed with their view that the essential nature of the change in tooth structure was the formation of fibrous tissue and was a degeneration. He considered that the changes were the result of a metaplasia of the cells tending toward the formation of new pulp tissue together with bone and produced by actively growing cells of an osteoblast type. The normal pulp is replaced by tissue resembling mature connective tissue. The complete fibrosis with no trace of cellular activity, as described by Zilva and Wells, has never been seen by Höjer.

A summary of the various changes in tooth structure in varying degrees of scurvy as described by Höjer may be given as follows:

Bone changes. The bone of a jaw already calcified at the onset of scurvy becomes porous through spaces forming in the marrow spaces and bone canals. There is a formation of new bone, chiefly on the outer surface of the bone, but also as connecting tracts within the marrow spaces. This new bone is deficient in collagen and inferior in quality.

Tooth changes. 1. The gradual change in appearance and eventual disappearance of the odontoblasts is the first sure sign of scurvy.

2. Amorphous calcification of the predentine occurs with absence of tubules in this layer.

3. The dentine already calcified at the onset of scurvy becomes porous through a dilatation and confluence of the dentinal tubules.

4. There is a formation of spongy bone-like tissue in the pulp instead of dentine.

5. Dilatation of the vessels and haemorrhages in the pulp.

6. Necrosis of the pulp and hydroptic changes.

7. Resorption of the pulp bone and dentine; atrophy of the pulp tissue appearing after the new formation of the bone in the pulp has stopped.

8. In scurvy, latent or mild in character, the changes in the teeth are similar though not so pronounced.

9. With doses of from 0.5 to 0.7 of the minimum protective anti-scorbutic dose, the irregular dentine laid down is tubular but in the lingual part of the tooth pulp there are symmetrically arranged ridges of pulp bone with canals. The hard tissues contain bone canals and in some places enclosed cells which later may be transformed into dentine.

10. With more than 0.8 of the anti-scorbutic dose there is no formation of pulp bone, but the newly-formed tissue in the pulp resembles osteodentine.

Criticisms of Höjer's work.

Höjer's work was the fullest account of experimental scurvy which had then appeared. It has not escaped criticism, although all succeeding workers have supported his main contention that the earliest changes

indicative of scurvy in the guinea-pig appear in the teeth. S. B. Wohlbach and P. R. Howe[17], in 1926, criticized Höjer's findings in several important respects and provided an ingenious explanation of the mechanism of the changes in the teeth. These workers believe that Höjer's findings were based on incomplete scurvy. They did not find any formation of pulp bone or osteodentine and considered that Höjer's diets were not completely deficient in the anti-scorbutic substance, for they found that appearances resembling those described by Höjer only occurred in guinea-pigs fed alternatively on a normal diet and a defective diet. They regard the histological appearance as representing the healing process induced by giving a dose of anti-scorbutic substance, instead of being due to scurvy as believed by Höjer. In complete scurvy Wohlbach and Howe described changes in the odontoblast layer occurring in from seven to twelve days and affecting the apical end of the tooth. The earliest change was a separation of the layer of odontoblasts from the dentine by a narrow margin. There were occasional deposits of calcium in the odontogenetic zone (predentine) and irregularities of the odontoblasts. The individual cells became smaller and stained more densely. The blood vessels in the pulp and the capillaries penetrating the odontoblast layer were more apparent. Occasional deposits of a basic staining material were seen, which Wohlbach and Howe interpreted as being due to calcium salts, while between the processes of the odontoblasts the evidence of continued dentine formation could be inferred from the presence of hyaline globules which they regarded as the matrix of calcospherites. After a longer period than twelve days there was a complete separation of the odontoblasts from the dentine with rupture of their processes, while the spaces between the odontoblasts and the dentine were unstained. These spaces resembled vacuoles and the authors concluded that they were caused by the accumulation of liquid material. The odontoblasts were smaller and stained more deeply. The pulp was oedematous and in places a deposit of finely granular material was seen between the connective tissue cells which might possibly represent an early deposit of calcium salts. Finally, in complete scurvy there was a picture of a shrunken pulp completely detached from the dentine and apparently floating in a liquid material. Contrary to the findings of Höjer, no bone was present and the new formation of intracellular matrix of bone and dentine had ceased. The administration of orange juice resulted in the prompt appearance of new dentine. In 24 hours, 2 c.c. only of orange juice given to a guinea-pig kept for twelve days on a scorbutic diet, resulted in the formation of a zone of dentine on the separated odontoblasts. A dose of 8 c.c. daily of orange juice for three days brought about a complete filling of the space between odontoblasts and dentine in scurvy of long standing. It was found that the newly-formed dentine might be thicker than the original dentine and that it followed the irregular contours of the odontoblast layer, which were due to the development of scurvy. This filling up of the space by dentine proceeded from the surface of the odontoblasts. Its rapidity and appearance before any discernible change in the cells indicated that the process

was one of setting or gelling of a liquid material. Wohlbach and Howe concluded that the liquid separating the odontoblasts and the dentine was a defective secretion of the cells formed in excess of the normal rate. This explanation accounts for the larger volume of dentine as compared with the original tissue. The missing factor which the anti-scorbutic agent enables the odontoblasts to supply is evidently one affecting the gelling of the liquid. Wohlbach and Howe characterize the condition of scurvy as being an inability of the supporting tissues to produce and maintain the intercellular substance. They advance the theory that the failure of cells to produce an intercellular substance in scurvy is due to the absence of an agent common to all supporting tissues which is responsible for the setting or gelling of a liquid product. This reaction may possibly be reversible.

Recent work.

The latest important work on the changes in the teeth in experimental scurvy was reported by E. W. Fish and L. J. Harris[3] in 1934. One important point made by these workers is that since the teeth of the guinea-pig are of persistent growth, sections at different levels may show the dental tissues in an embryonic stage, in a state of maturity or in a condition of senility and degeneration. When a tooth is examined to determine the local result of a special diet it is important to know which part was already formed when the special diet began to take effect and that which was formed after this date, since the structural effects of hypovitaminosis on the hard tissues are restricted to the part of the tooth formed after the diet has affected the metabolism of the animal. For this reason these workers used longitudinal sections of a fold of a cheek tooth and not transverse sections of the incisor teeth as used by Höjer and others. This obviates the fallacies which may result from using transverse sections of the incisor teeth which can show at one level odontoblasts in full activity and at a higher level cells in a state of degeneration. In fact the changes described as due to scurvy may be found occurring in various parts of the same tooth in a normal guinea-pig. Unless it is possible to ensure that a transverse section of an incisor tooth goes through a part of a tooth which has been formed subsequently to the ingestion of a diet deficient in vitamin C so that the results are a true index of the changes induced by that diet, then the findings may be open to suspicion. Another point of significance made by Fish and Harris is that secondary dentine is normally laid down at the senile, i.e., apical, end of the incisor teeth and that this tissue is identical with the ' osteodentine ' described by Höjer as a result of ' subscurvy.' They describe the effects of scurvy in the guinea-pig as an acceleration of the process of degeneration which occurs normally at the apical end of the teeth where the pulp cells have finished their active function. But instead of the senile odontoblasts at the apex dying, the younger odontoblasts all the way down the pulp also share in this change and become sealed off by a barrier of calcific tissue. In

' subscurvy ' the connective tissue cells remain alive for a time, but degeneration sets in and their fibrils become detached and a deeply staining deposit of calcium salts is laid down over the ends of the dentinal tubules which seals them off from the pulp. Lime salts are formed throughout the pulp in a collagen matrix which encloses islets of the degenerating cells and resembles the normal calcific material at the senile end of a healthy tooth. In fully-developed scurvy the phenomena are modified because the pulp is more severely affected. All the odontoblasts die as well as the primary dentine. This latter is sealed off by a deeply stained barrier of lime salts. But the pulp is unable to continue to react and lays down a collagen matrix as in ' subscurvy.' Even at the developing end of the tooth where cellular activity is greatest, no primary dentine is formed but only a narrow band of amorphous lime salts.

In addition to the modifications in dentine and pulp, Fish and Harris find changes in the ameloblasts (enamel-forming cells). These are, however, affected later than the odontoblasts. In ' subscurvy ' the enamel continues to form without appreciable change. But in fully-developed scurvy it completely fails to do so. The ameloblasts either disappear or become keratinized so that if the animal is cured by being given a fully protective dose of anti-scorbutic substance, there will never be any enamel on that part of the tooth which was forming when the scurvy was at its height. The cementum, by which a tooth is fixed into the jaw bone, is affected similarly to the dentine and its formative cells in the periodontal membrane degenerate like the odontoblasts.

The pulp-bone or osteodentine theory of Höjer is severely criticized by Fish and Harris, who argue with much force that this tissue is not bone and not an essential sign of ' subscurvy.' They regard it as secondary dentine which acts as a scar or barrier to dentine which has died and is part of the protective mechanism which occurs in every tooth undergoing irritation, whether physiological or pathological. A similar formation can be induced in a tooth by mechanical injury to a growing tooth. For these reasons Fish and Harris reject the view that the formation of ' pulp-bone ' is a neoplastic growth specific to scurvy.

If these views, which correspond in essentials to the earlier work of Wells and Zilva and of Wohlbach and Howe, are to be accepted then the elaborate series of changes described by Höjer in scurvy, incomplete scurvy and healing scurvy, must require modification. But even if Höjer's work be open to doubt in many of its details, yet his very complete investigations still remain of value. It provided clear proof of the early effect of scurvy on the teeth and gave a great impetus to other work on the subject.

Biological testing.

An interesting development of Höjer's work is its application as a means of testing the anti-scorbutic potency of various foodstuffs by noting the changes produced on the teeth of experimental guinea-pigs. A series of

papers by Höjer[8] and other workers appearing from 1926 onwards testify to the scope of this method of biological assay of anti-scorbutic potency. Höjer's technique may be summarized as follows:

Young guinea-pigs from a certain day are fed on a basal diet free from anti-scorbutic factors but otherwise complete. To this diet is added quantitative daily doses of the juices to be examined. Controls of animals on the basal diet alone and others on fully-protective dose of a known anti-scorbutic are also used. After ten to fourteen days all the animals are killed. The jaws are decalcified and a cross-section of the incisors examined. Höjer has formulated a series of changes affecting the odontoblasts, predentine and dentine, corresponding to various degress of scurvy thus induced. A value of one is given to a fully protective dose and corresponds to the appearance in a normal tooth. Höjer claims that by this method it is possible to graduate accurately degrees of protection less than the full and ranging from 0.9 of the protective dose to complete scurvy, which is given the value of 0. Clinically, Höjer has found this method useful. In February, 1925, he examined the anti-scorbutic value of milk sold as suitable to the Children's Hospital in Stockholm. A dose of 100 c.c. of this raw milk was given to each of four guinea-pigs. The histological picture showed that the amount was equivalent to 0.1 to 0.2 of the fully protective dose of a known anti-scorbutic. He concluded that 18 to 36 pints in the case of children represented a fully protective dose. In the summer when he tried to get rid of the anti-scorbutic substance in the milk by treating it with heated air for one hour there still remained so much vitamin C that the fully protective dose was only 4 to 7 pints per child. By this test Höjer concluded that winter milk may be deprived of its vitamin C but not summer milk. A similar experiment was made using Northern wild cloud berries which were shown to have as high an anti-scorbutic value as orange juice.

Höjer claims for this method of biological assay that it is accurate in fixing the full protective dose of any foodstuff and only requires three weeks as against three months by other methods. The appearance of this paper led to a considerable number of other works in which his method of assaying the anti-scorbutic potency of foodstuffs has been employed. M. Goettsch[4], using Höjer's method, confirms its accuracy and finds that it is more reliable and delicate than the method of estimating the development and degree of scurvy by such changes as the length of survival period, presence of stiff joints, or microscopical signs at autopsy such as haemorrhages into the joints and enlargement of ribs. By Höjer's method the minimum protective dose of sweet orange juice is 3 c.c. and only 1.5 c.c. by the old method. Goettsch, however, found that there was a considerable variation in the appearances of the teeth. While it was possible to estimate the minimal protective dose with accuracy, such variations in the teeth occurred in any one group of experimental animals on any one inadequate diet that the value of an inadequate diet could not be determined without using a large number of animals.

G. Dalldorf and C. Zall[1], instead of using differences in the structure of teeth to estimate anti-scorbutic values, studied the rate of growth of the persistently growing incisor teeth of guinea-pigs. They claim that in scurvy the teeth grow more slowly than in normal animals. The rate of growth of the teeth was studied by clipping exposed portions of one of

the lower incisors for varying periods from 20 to 90 days. The normal rate of growth was established by using animals on a standard basal diet with the addition of cod-liver oil. In the group of animals free from scurvy the rate of growth was 0.850 mm. daily in contrast to a minimal rate of 0.306 mm. daily in controls. It was found that in every case the addition of vitamin C increased the rate of growth and that deficiency of the vitamin slowed the growth. In an earlier paper, Dalldorf[2] described the lesions in skeletal muscles in experimental scurvy and showed that exercise and stress determined largely the location and degree of scorbutic lesions. Since an amputated tooth is subject to less stress than a tooth used for gnawing, Dalldorf and Zall studied the changes in the roots of the teeth. They found them similar to those described by Wohlbach and Howe. In complete vitamin deprivation the odontoblasts continued to regress and eventually changed into spindle and stellate forms resembling fibroblasts. If the diet contained only a small amount of vitamin C complete regression of the odontoblasts did not occur and instead of fibroblasts the cells came to resemble osteoblasts and formed an intercellular matrix similar to bone within the pulp. (This may explain the apparent discrepancy between the observations of Zilva, Höjer and Wohlbach and Howe.) Finally, in the late stages the pulp is filled with osteodentine. If the tooth has been clipped the evidence of scurvy both in the amount of osteodentine and the character of the cells, is less pronounced than in the unclipped tooth. This was true of all animals examined. In discussing these results Dalldorf and Zall state that the findings show that the scorbutic process is characterized by the inability of certain cells to form the intercellular substance natural to them. In partial deficiency an inferior substitute material may be formed less highly differentiated than dentine. When deprivation is complete the cells alter still further and form the still more primitive fibrous tissue. This process is similar to that occurring in long bones and costo-chondral junctions where osteoblasts appear unable to form bone matrix and become fibroblasts. With regard to the rate of growth of teeth Dalldorf and Zall conclude that there is a constant rate of growth of the incisor teeth in guinea-pigs in health. The deprivation of vitamin C causes the teeth to cease growing; the readministration of the vitamin restores growth to a degree roughly proportional to the dose of the vitamin. They suggest that under the standard conditions used for testing foodstuff for vitamin C the rate of tooth growth would appear to be a precise indication of the degree of scurvy, being more delicate than Sherman's method and more constant as well as more simple than Höjer's technique.

Using Höjer's method and its further elaboration by Goettsch, G. M. Key and G. K. Elphick[12] have described a quantitative method of estimating vitamin C for which they claim great delicacy. If, as must be assumed, the normal structure of the teeth is entirely dependent on the presence of vitamin C in the diet, it follows that the degree of scurvy produced can be graded to doses of vitamin C, provided that sufficient animals are given each dose in order to eliminate differences due to individual variations.

If a relation could be found between the average amount of protection given by a dose of vitamin C and the dose itself, then the dose which would produce full protection could be calculated for an unknown substance. Key and Elphick determined the anti-scorbutic potency of graded doses of orange juice on the lines laid down by Höjer and Goettsch.

The experimental animals were divided into groups which received graduated doses of orange juice varying from 0 c.c., 0.75 c.c., 1.5 c.c. to 3.0 c.c. daily. The feeding was continued for fourteen days and the animals were killed. The appearances at autopsy showed that some difference could be found in the conditions of the joints, etc., between animals fed on a scorbutic diet and those receiving orange juice, but it was not possible to differentiate between the effect of varying doses of orange juice. Sections were made of the incisor teeth and the tissues examined. In order to determine the numerical value for the degrees of scurvy produced in each animal an arbitrary scale was devised in which values from 0 to 4 represented stages from severe scurvy to complete protection. These four stages depended on the appearance of the odontoblasts, the band of inner dentine, and the development of the predentine. Key and Elphick found that nearly all animals fitted into one of these groups though a few exceptions were found in which one part of the tooth indicated severe scurvy while other parts would justify inclusion in intermediate groups. Such sections were judged independently by two workers and an average degree of protection determined. It was found that the teeth of all animals having no orange juice showed severe scurvy. A dose of 3 c.c. of orange juice conferred complete protection in eleven out of fourteen animals. The effects of intermediate doses was more variable but it was assumed that the average value for fifteen guinea-pigs receiving each dose of juice represented the true protective power for that dose as determined by the arbitrary scale. The average dose plotted for the degree of protection from scurvy and plotted against the dose of orange juice gave a straight line. This curve could be used to compare any unknown substance with any standard. Key and Elphick claim that this method is more accurate than that used by Höjer and is particularly useful in determining the potency of substances containing little vitamin C.

Changes in other animals.

It will be noted that all the investigations here described deal with the effect of deficiency of vitamin C on guinea-pigs. Apart from the susceptibility of this animal to scurvy which makes it so suitable for experimental work, it has teeth which grow from persistent pulps, a condition quite different from man and most mammals whose teeth are of limited growth and once formed can undergo but slight changes. For this reason it is difficult to draw conclusions which could be applied to the dental tissues of man. Experiments on dogs, whose teeth resemble those of man in being of limited growth, have failed to show that vitamin C has any effect on the teeth. Mrs. Mellanby[13] for that reason concluded that it was improbable that the actual structure of human teeth was greatly affected by a deficient intake of vitamin C. It is, however, significant that L. J. Harris has shown that dogs, unlike humans, monkeys and guinea-pigs, do not require vitamin C. They can synthesize it in their bodies and therefore cannot suffer from vitamin C deficiency. The experiments on guinea-

pigs as an index of what might happen in man, while of interest, fail in the important condition that the teeth are constantly being formed throughout life. This means that the pulp which is the formative tissue of the dentine is always of high functional activity, whereas in man once the dentine, is formed the pulp retains only a low degree of formative power. Thus any changes which may be induced by a deprivation of vitamin C are not likely to be shown in the teeth of man in the same way as in the teeth of persistent growth in guinea-pigs. This does not mean that a deficiency of vitamin C may not be without effect on the health of the dental tissues of man but it increases the difficulty of estimating such changes if they exist. It is significant that the latest workers on the subject, Fish and Harris, propose to continue their investigations on monkeys whose teeth anatomically and physiologically closely resemble those of man.

The view has been expressed by Howe and others that a deficiency of vitamin C may be responsible for lesions of the supporting tissues and lead to pyorrhoea, partly on the evidence of loosening of the teeth in guinea-pigs suffering from scurvy and partly on the clinical investigations carried out by Hanke[5] and a group of clinicians.

G. Westinn[16] who has collaborated with Höjer in the latter's investigations, regards their findings in guinea-pigs as being valid for man. He finds evidence of the formation of masses of calcified tissue in the pulps in cases of human scurvy and considers that these are identical with the pulp-bone described by Höjer as a sign of scurvy in guinea-pigs. Metaplastic changes in the pulp with regression of odontoblasts and the formation of osteoblasts and fibroblasts may also be found. He would apparently go farther and regard these pulp changes as likely to indicate the presence of latent scurvy and to possess a diagnostic significance. But these masses of calcified tissue in the pulp of human teeth have long been known and are not uncommon. Similarly, changes in the pulp of a regressive nature are extremely common and occur as a reaction to caries. It is conceivable that in cases of human scurvy changes in the teeth comparable, so far as the different anatomical conditions permit, to those found in scorbutic guinea-pigs may also be present. But the reverse inference that these pulp changes, when present, are a sign of scurvy seems to be a proposition which has little to support it. M. Ohnell[14] has also described cases of human scurvy with a formation of pulp stones and suggests that they possess diagnostic significance. He concludes that a generalized formation of pulp stones as demonstrated in x-ray pictures, should at once arouse a suspicion of scurvy. Here again, the chain of evidence seems too weak to carry such a generalization.

The work of Hanke[5] represents the most ambitious attempt to found a dental pathology of scurvy in man on the effect of vitamin C deficiency. Hanke and his fellow workers claim to have cured cases of pyorrhoea by giving massive doses of orange juice. They found that children fed on a quart of milk, one-and-a-half ounces of butter, a pound of vegetables, half a pound of fruit and an egg a day, may develop dental caries and

gingivitis. The addition of a pint of orange juice and that of one lemon to this diet supplied something which led to a disappearance of most of the gingivitis and an arrest of 50 per cent. of the caries. It would be easy to criticize this work and to point out that a diet containing such a large amount of vegetables and fruit would scarcely be likely to be deficient in vitamin C. The inference which might be drawn, namely, that the orange and lemon juice by virtue of its vitamin C supplied the necessary ingredient which reduced the liability to gingivitis and arrested the process of dental caries, might therefore be open to question. If the clinical results of giving orange and lemon juice as a supplementary ration to a diet which otherwise appears sufficient, are as stated by Hanke, then some other explanation must be sought. But while clinical investigations such as these must necessarily lack the precision of controlled laboratory experiments, they cannot be easily dismissed. It is probable that among many civilized communities vitamin C is likely to be deficient and the possibility must not be overlooked that minor deficiencies of this vitamin exist which fall short of actual scurvy but are sufficient to lead to impairment of the integrity of the dental tissues and thus predispose to dental disease.

Summary.

Scurvy in guinea-pigs is easily produced by withholding vitamin C. Changes varying from slight alterations in the dentine and odontoblasts can be caused by deficiency of this vitamin. The result of complete scurvy leads to an entire disintegration of the cellular elements (Zilva and Wells). It is agreed by all workers that the earliest signs of scurvy are found in the teeth before any clinical signs are present. A sequence of changes in mitigated scurvy are described by Höjer which lead to the formation of bony tissue in the pulp. Wohlbach and Howe, and Fish and Harris both agree in denying the validity of these observations of Höjer. According to Fish and Harris this calcific tissue is the result of irritation comparable to the changes induced by mechanical irritation both in man and experimentally, and have not the significance of a metaplastic formation as postulated by Höjer. A further point of some importance made by Fish and Harris is that as the teeth of the guinea-pig are of persistent growth, cross-sections will show varying phases of functional activity at different levels in the same tooth and that some of the appearances assumed by Höjer to be due to vitamin C deficiency may well be normal for that particular stage of formation in the cross-section of the tooth examined. To get over this fallacy Fish and Harris have used longitudinal sections of the molar teeth so as to get a picture of the pulp at its different levels of senility at the tip, maturity in the middle of the tooth and active development at the open end of the root. By this method they claim to have obtained a true picture of the changes produced by vitamin C deficiency. They regard the effects of scurvy on the teeth as being an acceleration of the process of degeneration which occurs normally at the apical end of the teeth where the pulp cells have finished their active

function but which extends all the way down the pulp so that the younger odontoblasts are affected and react by becoming sealed off by calcific tissue (the equivalent of the pulp-bone described by Höjer). They also find changes in the enamel-forming cells which in fully developed scurvy fail to form enamel. Wohlbach and Howe, as the result of their observations, find changes which finally result in a shrunken pulp completely detached from the dentine and floating about in a fluid. They regard this fluid as being a defective secretion of the cells formed in excess of the normal rate. The missing substance which the anti-scorbutic agent enables the odontoblasts to supply is one affecting the gelling of the liquid. Scurvy is in essence a condition in which there is an inability of the supporting tissues to maintain an intercellular substance. Chemical analyses of scorbutic teeth carried out by G. Toverud show that there is a reduction of ash and CaO and an increase of magnesium as compared with normal teeth. She regards the substitution of calcium by magnesium as being an attempt to maintain the amount of salt in the teeth when calcium is not available. A development of Höjer's work is the use which has been made by Höjer, Goettsch, Key and Elphick to estimate the anti-scorbutic efficiency of various substances by noting the effects on the teeth. Accuracy and speed of investigation are claimed for this method of biological assay. Dalldorf and Zall instead of relying on the histological changes in the pulp and dentine, have studied the rate of growth of the persistently growing incisors of the guinea-pig and find that in scurvy the rate of growth is diminished.

Conclusions.

In attempting to estimate the significance of this vast body of work on experimental scurvy one is faced with the difficulty that the experimental animal employed, the guinea-pig, differs in many important respects from man. The fact that the teeth are of persistent growth enables the effect of varying degrees of vitamin C deficiency on the dental tissues to be ascertained with ease since their formation proceeds pari passu with the action of the special diet on the organism. In man the teeth are of limited growth and thus any effect of scurvy on them, if it exists, cannot be demonstrated in the same way for tooth formation has already stopped. The dog, which as regards the teeth might behave like humans, is ruled out since it is not susceptible to scurvy. So far the monkey, which should provide the closest analogy to man, has not been used. How far is it possible to apply the results of the experiments on guinea-pigs to man with the implication that deficiency of vitamin C may be responsible for some aspects of dental disease? Hanke and his fellow workers have boldly drawn the conclusion that both gingivitis and dental caries may be affected by a lack of vitamin C and they claim that by giving massive doses of orange and lemon juice both these forms of dental disease can be greatly lessened. It would probably be agreed by dieticians that among many civilized communities there is often a

shortage of vitamin C in the diet. In scurvy, whether affecting adults or children, the disease affects the supporting structures of the teeth and leads to gingivitis and progressive loosening: changes which are in many respects comparable to pyorrhoea. But florid scurvy of this type is now rare. The real interest in vitamin C, as with other vitamins, is not so much the results of complete deprivation as the question as to whether relatively small deficiencies may predispose to various impairments of health. Is there any evidence that there is a tendency for children to suffer from a shortage of this vitamin and if so, may it be a factor predisposing or actual in the incidence of dental disease? To this question no decisive answer can be given. The work of Hanke is interesting and suggestive. Though lacking in complete proof yet taken in conjunction with the experimental work described, it suggests that vitamin C as well as vitamins A and D may be necessary to a normal development and function of the teeth and that any deficiency of this vitamin in the diet may be reflected in a lowered resistance of the teeth to disease. Since the average dietary may easily be deficient in vitamin C it is desirable to emphasize the importance of ensuring a plentiful supply of this vitamin during the all-important years of childhood when growth both of the teeth and other tissues is most active and when the susceptibility to dental disease is greatest.

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MALNUTRITION AND LATENT SCURVY

BY

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All investigators who have pursued the study of infantile scurvy, whether clinically or experimentally, have based their work upon Sir Thomas Barlow's classical description of the disease, and the light thrown by him upon its causes. The thoughts and ideas put forward by him in 1883 have received their final confirmation through modern scientific investigation.

Simultaneously with this, our knowledge of the clinical manifestations of the complaint has been extended, so that we can now also recognize cases of infantile scurvy that do not exhibit the typical symptoms characterizing the cases forming the basis of Barlow's description, which can never be forgotten by anyone who has had an opportunity of studying his fine collection of pathological-anatomical preparations.

The now well-known slighter cases of infantile scurvy show themselves by a more or less pronounced dystrophy, accompanied by anorexia, anaemia, occasionally by slight oedema, cessation of gain in or loss of weight, reduced power of resistance against infection, intestinal disturbances, but now and then also with more pronounced scorbutic symptoms, particularly haematuria (erythrocyturia minima), which in pronounced cases of scurvy in infants is one of the earliest, and in the opinion of many, the most common symptom of scurvy. On the basis of the symptoms here specified, it is possible in most instances, with a certain degree of probability, to recognize the majority of cases of pre-scorbutic dystrophy, but a definite diagnosis is only obtained ex juvantibus, when the child is given vitamin C, which has specific and rapid effects in such cases.

The usual assumption has hitherto been that infantile scurvy makes its first appearance in the latter half of the first year, and this has been justified so far as it concerns the typical clinical cases, but there is no doubt that slighter, pre-scorbutic dystrophy may occur earlier if the child's mother has been nourished on food deficient in vitamin C, or if the child's diet from the beginning has been deficient in vitamin C. In particular the latter factor

may be of importance if on account of gastro-intestinal troubles the child has not been able to assimilate the vitamins administered, or if the child's need of vitamins is increased on account of acute or chronic infections.

Far less known, at any rate in northern countries, is the occurrence of slight, latent forms of beri-beri in small children, and this is no doubt mainly due to the difficulty in making a diagnosis, because here a specific symptom, like that of haematuria in scurvy, is lacking. It is a question, however, whether scorbutic dystrophy when accompanied by well-marked oedema, without any affection of the heart or kidneys, should be regarded as also dependent upon a lack of vitamin B. In this connection it should be remembered that A. Holst and Frölich[1] found that in pigs a diet deficient in both vitamins B and C could produce a clinical picture characterized by haemorrhages, oedema and typical degenerative nerve changes; the clinical picture was regarded as that of a mixed form of scurvy and beri-beri. It was precisely this experimentally-produced mixed form that led me to regard the following case as an example of dystrophy, conditional upon a lack of both vitamins B and C in the diet.

Case record.

The patient was a girl, three months old, born at full term on July 17, 1934. She was of ordinary size and weight (not weighed at birth), and was breast fed for the first two months, subsequently being given daily only 500 c.c. of a mixture consisting of equal parts of milk, oat-meal gruel plus 20 gm. of sugar. For the last fourteen days before admission she received cod-liver oil, one teaspoonful, three times daily.

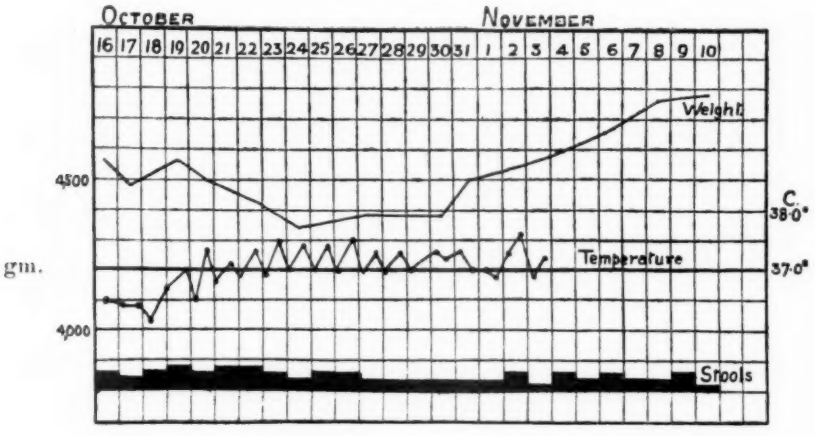
With this diet the child vomited after nearly every meal, and passed two to three times daily, thin, viscous, greenish stools. Simultaneously she had severe dermatitis (erythrodermia desquamativa, Leiner).

After one week on this diet, the child became swollen in the face, and later on there appeared swellings in her legs and back. She became markedly pale and listless.

On admission to hospital (October 16, 1934) the child was extremely debilitated, screamed with a weak, whimpering voice, presenting a poor turgor and tone. Her weight was 4,450 gm., length, 55 cm., temperature, 36·5° C. Her red corpuscles numbered 4,010,000 per c.mm., the white corpuscles, 14,200 per c.mm. Haemoglobin was 70 per cent. (Sahli). Röntgen examination showed a normal skeleton. The liver was slightly enlarged, the spleen was not enlarged. She presented the picture of an erythrodermia desquamativa. The skin of her face was swollen with a cutaneous oedema. The lower extremities were greatly swollen with an extensive cutaneous oedema showing pitting on pressure. The skin was tight and shiny.

The urine contained no albumin, sugar or pus; on the other hand, microscopic examination revealed a few red corpuscles, and some days later the urine also gave a positive reaction with the benzidin test. October 26, the oedema and haematuria had disappeared. On November 3 the urine was normal, and also on November 10.

On the last date the patient was discharged in a good general condition, increasing in weight (to 4,780 gm.), and in length, 57 cm. (increase 2 cm.). The skin was normal, oedema had disappeared, the stools were normal, and the urine normal.



Discussion.

The diet upon which the patient became ill was calorically inadequate and insufficient with regard to albumin, amino-acids and mineral substances. In addition, it was very deficient in vitamins B and C, whilst during the last fourteen days it contained sufficient vitamins A and D.

It therefore appeared reasonable to explain the entire clinical picture, the acute gastro-enteritis, the dermatitis, haematuria and oedema, as a result of the entirely insufficient diet, a view that received strong support by the rapid improvement that took place after the employment of the following diet:—

The child was given 600 gm. of milk mixture (2 parts milk, 1 part water), to which were added 24 gm. of sugar, 15 gm. of cod-liver oil, 15 gm. of malt extract and 15 gm. of orange juice. Thereby the caloric requirements were covered by 120 cal. per kgm. of bodily weight and the requirements of vitamins satisfied for all the necessary vitamins concerned.

On this diet the severe gastro-enteritis immediately improved, the oedema disappeared in the course of ten days, with a loss in weight of 230 gm., after which the patient increased in weight by 460 gm. in sixteen days. The haematuria also disappeared in the course of ten days, the dermatitis was quickly cured and the general condition was very good.

This rapid alteration in the clinical picture gives strong support to the view that the patient's illness should be regarded as a deficiency disease resulting from an insufficient supply of vitamins C and B.

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THE VITAMIN C CONTENT OF THE LIVER OF NEWBORN INFANTS

BY

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Until recently workers have been entirely dependent on feeding experiments in order to determine the amount of vitamin C present in tissues. This method, however, is difficult to apply to the study of small amounts of tissue, neither is it possible to study in this way the small variations of the vitamin C content of the different organs. After the identification of ascorbic acid as vitamin C, verified by nearly all investigators, the development of a direct chemical method for the estimation of this substance in small amounts of tissue has made possible a new approach to the study of the storage of vitamin C in the human organism. It is known, however, that the chemical reaction is not absolutely specific for the vitamin present. Nevertheless this method gives in a very short time a more precise measure of the vitamin content of the tissue than feeding experiments, even if large quantities of tissue are used and a long time is spent on the performance of the animal experiment.

During the last two years the livers from fifty-six new-born infants have been examined as to the ascorbic acid content. The method used was learnt in the Nutritional Laboratory of the University of Cambridge and is described in detail by Birch, Harris and Ray[1]. The ascorbic acid used for the titration of the 2 : 6 dichlorphenolindophenol was very kindly sent me from the British Drug Houses Ltd., London.

Of the fifty-six new-born infants examined thirty-one were full-term infants and twenty-five were premature infants.

From table 1 it will be seen that the ascorbic acid content varies from 2·7 mgm. to 10·4 mgm. per 100 gm. of fresh liver substance. These two extreme figures represent only two cases, no. 134 and 142 of the premature infants. Most of the other cases show about 6 and 7 mgm. per 100 gm. of liver substance. The average figure is 6·05 mgm. for premature infants and 7·01 mgm. for full-term infants.

The normal ascorbic acid content of new-born infants' tissues is not yet known. Only a few studies are available in the literature of ascorbic acid-content of human tissue. One of these is by Yavorsky, Almaden and King[2], who found the average figure for liver from infants one to thirty days old is 14·9 mgm. per 100 gm. of tissue. They noted great variation from one

TABLE 1.

FULL-TERM INFANTS.

No.	Weight: gm.	State of infant	Ascorbic acid: mgm. per 100 gm. of liver	Mother's condition during pregnancy	Findings at autopsy.
105	2800	Stillborn	7·0	Poor diet, bleeding	Cerebral haemorrhage
108	3600	,,	8·0	Poor diet	Perforation
111	4200	,,	9·3	Poor diet	Perforation
112	4700	,,	7·4	Good diet	Perforation
113	4500	,,	5·6	Average diet	Perforation
115	3530	,,	8·8	Good diet	Perforation
118	3500	,,	4·9	Good diet	Nil
121	3330	Lived ½ hr.	6·7	Poor diet, mother anaemic	Nil
123	4300	Stillborn	6·2	Poor diet, mother anaemic	Perforation
127	3430	Lived 3 days	7·1	Good diet, felt well	Cerebral haemorrhage
129	3170	Stillborn	7·4	Good diet, hypertension, albuminuria	Cerebral haemorrhage
131	3630	Lived 5 hr.	6·1	Poor diet, felt well	Nil
137	2900	Lived 3 hr.	3·3	Poor diet, haemorrhage, Caesarian section	Cerebral haemorrhage
138	4000	Stillborn	8·1	Good diet, slightly anaemic	Cerebral haemorrhage
139	2850	Lived 28 hr.	7·6	Average diet, albuminuria	Bronchopneumonia
140	3410	Stillborn	7·5	Good diet, felt well	Perforation
141	3000	,,	6·9	Average diet, felt well	Maceration
143	3500	,,	6·0	Good diet	Perforation
144	3470	Lived 2 days	9·0	Good diet	Haemorrhage in spinal canal
147	3800	Stillborn	7·3	Average diet	Cerebral haemorrhage
148	3540	,,	5·8	Poor diet, bleeding	Perforation
150	3500	,,	6·9	Average diet, mother anaemic	Perforation
151	4070	Lived 6 days	6·4	Poor diet, mother anaemic	Cerebral haemorrhage
152	3690	Lived ½ hr.	6·3	Average diet, felt well	Cerebral haemorrhage
154	3680	Stillborn	7·6	Average diet, felt well	Nil
155	3100	,,	6·0	Average diet	Maceration
156	3050	,,	7·4	Average diet	Nil
157	2800	,,	8·1	Average diet	Nil
158	3360	,,	7·5	Good diet	
163	3450	,,	8·0	No information on diet	Perforation
164	4830	Lived 4 days	7·1	No information on diet	Cerebral haemorrhage Adrenal haemorrhage

TABLE 2.

PREMATURE INFANTS.

No.	Weight: gm.	Age of foetal life in weeks	State of infant.	Ascorbic acid: mgm. per 100 gm. of liver	Mother's condition during pregnancy	Findings at autopsy.
103	1600	34	Stillborn	7·4	Average diet, albuminuria, anaemia	Nil
104	2000	36	,,	6·0	Poor diet, chronic nephritis	Nil
106	1670	34	Lived 24 hr.	6·6	Average diet, unmarried	Cerebral haemorrhage
107	1500	32	Stillborn	8·2	Good diet, hypertension	Spinal haemorrhage
117	1600	30	,,	5·5	Good diet, felt well	Nil
120	1600	30	Born alive	5·8	Poor diet	Broncho-pneumonia
122	1230	30	Stillborn	5·7	Average diet, bleeding, anaemia	Spinal haemorrhage
124	1390	30	,,	4·9	Poor diet, bleeding, Caesarian section	Cerebral haemorrhage
125	2440	34	,,	4·4	Poor diet, hypertension	Spinal haemorrhage
126	1900	36	,,	5·7	Average diet, eclamptic attacks	Cerebral haemorrhage
128	2250	36	Lived 2 hr.	8·6	Good diet	Nil
130	2830	38	Lived 3 days	6·2	Average diet, cystitis	Atresia ani
132	2100	36	Stillborn	7·6	Good diet, habitual abortion	Nil
133	2400	38	,,	6·6	Average diet	Nil
134	2220	36	,,	2·7	Good diet, felt well	Congenital heart defect
135	1400	30	,,	4·7	Average diet, eclamptic attacks	Nil
136	1760	32	Lived 8 hr.	6·2	Good diet	Cerebral & spinal haemorrhage
142	2530	38	Stillborn	10·4	Average diet, hyperemesis	Spinal haemorrhage
145	2770	38	Lived 8 hr.	8·0	Good diet, chronic nephritis	Nil
146	1300	32	Stillborn	8·5	Average diet, hypertension	Nil
149	1690	32	Lived 14 hr.	7·5	Average diet	Cerebral haemorrhage
153	1300	32	Born alive	7·4	Average diet, albuminuria, hypertension	Cerebral haemorrhage
160	2000	36	Stillborn	5·6	Good diet, hypertension	Cerebral haemorrhage
161	1400	30	,,	6·5	Uterine tumour, poor condition	Nil
162	600	26	,,	4·5	Good diet, habitual abortion	Nil

individual to another. These authors also found that the distribution of vitamin C of human tissue corresponds fairly well to data obtained from titration of guinea-pig tissues. Here the value found with early scorbutic symptoms was determined to be 3 mgm. as far as the liver is concerned.

In the findings of the present investigation the average figures of 6 and 7 mgm. were considerably lower than the average of the above-mentioned investigations, though it must be considered that these infants, one to thirty days old, may have had some antiscorbutic foodstuff given to them during the days of post-uterine life. There is only one infant in these authors' series which may be compared with the present cases, namely a still-born one, showing 11 mgm. One twenty-four days' old infant showed only 7·4 mgm., a figure nearly the same as the average figure of the full-term infants in the present series.

It is not yet known what must be accepted as the level of ascorbic acid content in the liver associated with scorbutic symptoms in children. If, however, according to the findings of the above-mentioned authors conclusions are drawn from the human and guinea-pig studies, 3 mgm. correspond with early scorbutic symptoms. In the present series there is one case with a value below this figure. Six more cases show values close to this, that is they are all below 5 mgm. per 100 gm. of liver substance. These seven cases may, then, be looked upon as suffering from latent scurvy. Of these infants only two were full-term, the other five were all premature infants.

When these infants with a vitamin content below 5 mgm. are considered in detail, it is seen from table 1 that the full-term infant no. 118 with an ascorbic acid content of 4·9 mgm. was born of a mother who received a good diet during pregnancy. No pathological findings were noted at autopsy. The other full-term infant, no. 137, with a low ascorbic acid content (3·3 mgm.) was born of a mother who received a poor diet during pregnancy and she had several haemorrhages the last fourteen days before delivery. The infant showed a small haemorrhage in the cerebral meninges at autopsy. As to the five premature infants, no. 124 (table 2) with an ascorbic acid content of 4·9 mgm. was born of a mother who had poor diet during pregnancy. A Caesarian section was performed on account of a premature separation of the placenta. At autopsy a large cerebral haemorrhage was found in the infant. The infant no. 125, with a content of 4·4 mgm. was also born of a mother who received a poor diet during pregnancy. This mother was suffering from a toxaemia with albuminuria during her pregnancy. At autopsy on the infant a haemorrhage was found in the spinal canal. The infant no. 134, with the lowest content found in this series, namely 2·7 mgm., had a severe congenital heart lesion. This infant's mother received a good diet during pregnancy. The mother of infant no. 135 showing 4·7 mgm., had a severe toxaemia with albuminuria and eclamptic attacks in the last part of pregnancy. The diet of the mother was an average one. As far as the last case is concerned, no. 162, this infant's mother

was suffering from habitual abortion (seven still-born infants previously). Her diet was good throughout pregnancy. The autopsy findings were negative.

It is thus found that with one exception—the full-term infant no. 124—the rest of the infants with the vitamin content below 5 mgm. per 100 gm. of liver substance, were born of mothers having had either a poor diet during pregnancy or having suffered from toxaemia or habitual abortion during this time or the infant itself was pathological in some respect. The conditions here mentioned may explain the low vitamin C content of the liver in these infants.

In eight cases other organs besides the liver have been examined. The content of the adrenals has varied from 10 to 13 mgm.; of the kidneys from 2 to 3 mgm.; of the thymus from 1 to 2 mgm.; and in one instance the lung was examined with the result of 5·18 mgm. per 100 gm. These values are all below those of Yavorsky, Almaden and King.

Such low values for the liver, as well as for the other organs, indicate that the vitamin C content actually is very low at birth in Norwegian infants. This fact has, therefore, to be considered, in the regulation of the pre-natal and post-natal diet of the mother and the child.

The early development of scorbutic symptoms, as demonstrated by Prof. Frölich at a meeting of the Norwegian Paediatric Society in November, 1934, consisting of haematuria in a three-months' old infant, disappearing on antiscorbutic treatment, can only be explained on the basis of a low congenital store of vitamin C in the organism. The time of development of symptoms of scurvy will depend partly on the congenital store of vitamin C present and partly on the deficiency of the post-natal diet. As a third factor has to be considered infections present in the infant's post-natal life. Here a vicious circle occurs as the infections are partly a result of the deficiency of the vitamins in the infant's organism. At the same time the infection, with the increased general metabolism and the low food intake and poor absorbtion, will contribute in lowering the vitamin store of the organism, and render the infants even more susceptible to different infections.

In such infants there is usually not only a deficiency of one vitamin but a general vitamin depletion. This has been confirmed by examining the storage of the vitamins A and D in a larger series of new-born infants, including those in this series. The storage of A and D has been low and in some infants hardly detectable. The result of these investigations will be published in a separate article.

Summary.

The ascorbic acid content has been examined in the liver of fifty-six new-born infants of which thirty-one were full-term and twenty-five premature infants.

The average value for the full-term infants was 7·01 mgm. and for the premature infants 6·05 mgm. per 100 gm. of fresh liver with variations from 2·7 to 10·4 mgm.

The significance of the low content of ascorbic acid at birth for the early development of scurvy in infancy is discussed.

I am indebted to Prof. Harbitz and Prof. A. Sunde for the opportunity of using the material.

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INVESTIGATIONS INTO THE PATHOGENESIS OF SCORBUTIC DYSTROPHY*

BY

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In 1883 Sir Thomas Barlow definitely established the nature of infantile scurvy and after a long period of hestitation, the scorbutic character of this affection is now universally recognized. The same author, in 1904, drew attention to the ' formes frustes ' of the disease and following this Alfred Hess gave a masterly description of these varieties. This latter author divided scurvy into an acute type, a subacute type and a third type characterized by a general disturbance of nutrition without manifest scorbutic lesions. This division corresponds exactly to what is observed in practice. It is not intended here to describe the history of scorbutic dystrophy, in the study of which a large number of authorities in different countries have collaborated. The essential features only will be described.

Apart from manifest scurvy, with its classical symptoms, there exists the variety of the disease in which the true nature of the uncharacteristic general disturbance is shown by the appearance of a specific tendency to haemorrhage with petechiae, haematuria, occult blood in the stools, tenderness over the bones and a positive tourniquet test. According to A. F. Hess the eyelids are puffy, the heart a little enlarged, the respiration rapid and the pulse rapid and variable. An antiscorbutic diet quickly causes the disappearance of these symptoms.

In prescorbutic dystrophy the confirmatory signs of the haemorrhagic tendency are absent. It is a state of chronic wasting, characterized by pallor, anorexia, change in character, a slowing-up of the increase in weight and also, rarely, of the increase in length. Sometimes chronic disturbances of digestion occur: other patients present an anaemia which only reacts to a combination of iron and vitamin C (Rohmer and Bindschedler[1]). A persistent rise in temperature may be met with, explained usually by slight, recurring infections. It is accepted by most authorities that in this condition there exists, in fact, a special susceptibility to infections, which are more frequent, of longer duration and more serious than among normal children.

This dystrophic state can precede the appearance of manifest scurvy, which, however, also often supervenes without any premonitary signs in a state of apparent perfect health. The symptoms of manifest scurvy have

* Translated by A. Moncrieff.

been observed appearing suddenly in infants who have been in-patients in the clinic for several months, where they have received the standard diet and have not shown the least symptom of dystrophy. It has often been ' brought out ' by an accidental cause, for example, by an infection such as whooping cough. In other instances, the major symptoms of scurvy do not occur at all. The scorbutic character of the dystrophy is only indicated by minor haemorrhagic symptoms which establish the diagnosis. In the majority of cases these minor diagnostic signs of a scorbutic affection are also absent. The commonplace state of wasting persists for a varying period and disappears gradually, generally when certain modifications are introduced into the child's diet as the age increases.

In experimental scurvy the guinea-pig, completely deprived of vitamin C, maintains at first the appearances of good health. In the early days the deficiency only shows itself by a slight diminution in appetite and in the increase in weight, until the moment when the manifest symptoms of the disease suddenly appear. It is equally possible to produce the syndrome of dystrophy in this animal if the intake of vitamin C is maintained for a definite period slightly below the necessary dose.

While the different varieties of experimental scurvy can be produced in the guinea-pig with an almost mathematical precision, it is quite otherwise in the child, in whom the pathogenesis remains obscure, obeying apparently very capricious rules, whose effect is unpredictable. It is certain that the requirements of infants for vitamin C vary enormously according to their age, their constitution, their general condition and their previous illnesses. This explains why, despite the fashion of sterilized milk which is still far from being always corrected by the addition of vitamin C, cases of scurvy are relatively rare. The frequency of prescorbutic dystrophy is unknown but it can be stated that this dystrophy only shows itself in a relatively small number of infants whose diet does not differ from that of the majority of babies who remain in good health and gain weight normally.

The recent discovery of the chemical nature of vitamin C—laevo-ascorbic acid containing a dienolic group (–COH : COH–), responsible primarily for its reducing properties—has not yet completely cleared up this difficulty.

In a communication made at the Third International Paediatric Congress (London, 1933), we announced our intention of studying the latent, prescorbutic state in infancy by means of certain methods, which one of us had introduced some years ago without their finding the widespread clinical application which they appeared to merit. In the first place we have used the method of testing the urine with monomolybdo-phosphotungstic acid. The following are briefly the details of procedure.

Preparation of standards.—The violet coloration which is given by monomolybdo-phosphotungstic acid with hydroquinone, pyrocatechin or vitamin C attains its maximum intensity when three molecules of reagent react with one molecule of this substance. This detail is important since certain other polyphenols, frequently present in organic substances, such as tannin, also contain a dienolic group which can give this reaction. But with

these the reaction is only produced in the presence of a large excess of reagent and is preceded by a yellowish-brown colour. It is therefore essential to gauge the amount of reagent so as to add sufficient but at the same time to avoid all excess. The reaction is given equally by vitamin C and by its immediate break-down product which still retains the dienolic group (probably a dienol-hexosic acid). Elsewhere[2] a method of differentiating these two substances has been described. For the purposes of the present investigation this differentiation is unnecessary.

As a standard hydroquinone has been used with the provision that in equal molar concentration the violet reaction of vitamin C is about 12 per cent. more feeble than that given by hydroquinone. This disparity is corrected by using in the preparation of the standard, 100 mgm. of hydroquinone instead of 110 mgm. which would correspond exactly with the molecular weight. The 100 mgm. of hydroquinone are dissolved in 100 c.c. of water and 1 c.c. of this solution is freshly diluted to 100 c.c. Of this second solution 1 c.c., 1·5 c.c. and 2 c.c. are placed in three test-tubes of colourless glass, marked to show 5 c.c. and 10 c.c. To each of the three tubes is added one drop of the reagent and 5 per cent. sulphuric acid is then added to the 10 c.c. mark. The reagent is prepared by dissolving 7·5 gm. of monomolybdo-phosphotungstic acid in sufficient dilute sulphuric acid (5 per cent. by volume) to make 100 c.c. (Another solution containing only 3·75 gm. of reagent is also prepared.) The reagent solution is kept in dropping bottles made of brown glass, giving 15 drops per c.c. If the standards are protected against the direct effect of light they maintain their colour without any notable change for two or three days.

The intensity of colour of the standard containing 1 c.c. of the solution of hydroquinone is equal to that produced by a solution of 10^{-5} N. ascorbic acid, containing 1·76 mgm. of this substance per litre. This colorimetric equality is indicated by the symbol ' U.H.' (' unité hydroquinol '). The intensity of the colour of the standards in the second and third tubes corresponds to 1·5 and to 2 U.H. respectively, that is to solutions of vitamin C of approximately 2·6 and 3·5 mgm. per litre.

Preparation of human urine for analysis.—The urine is first cleared. For this purpose the following clearing agent is utilized: 100 gm. of crystalline neutral lead acetate and 100 c.c. of glacial acetic acid are dissolved in distilled water to make 1 litre. To 20 c.c. of urine 12 c.c. of this clearing agent are added. Two minutes afterwards, without filtration, there should be added 8 c.c. of a solution containing 200 gm. of crystallized sodium sulphate ($Na_2SO_4 12H_2O$) per litre. This mixture is rapidly shaken and filtered through filter paper. The filtrate ought to be absolutely clear. Of this cleared urine 10 c.c. are placed in a test-tube exactly similar to those used for the standards and one drop of reagent is added. The total time for these procedures ought not to exceed twenty minutes.

Reading the results—If the urine tested is absolutely colourless after the clearing process and if the colour obtained with one drop of the reagent (7·5 per cent.) is equal to that in the third standard tube, this is equivalent to 2 U.H. The quantity of reagent contained in one drop is sufficient to produce a colour change equivalent to 3·5 U.H. so that in the example given there is sufficient reagent used but, on the other hand, not too much. The reading can therefore be regarded as correct. Since the urine was diluted by half in the clearing process the figure of 2 U.H. must be multiplied by two. This urine therefore contains, as vitamin C or its immediate break-down product, four times 10^{-5} N. which equals 7 mgm. of ascorbic acid per litre.

If the colour obtained is deeper than that in the third standard tube the urine must be diluted with equal parts of distilled water and test repeated. It frequently happens, with the urine of young, healthy infants, that the

urine has to be diluted eight times or even sixteen times. For such dilute urines it is preferable to use the weaker reagent (3·75 per cent.). The intensity of colour change finally obtained should not exceed that of the second standard tube, that is corresponding to 1·5 U.H. or 2·6 mgm. ascorbic acid per litre. This figure is multiplied according to the degree of dilution.

It may happen that after clearance the urine retains a slight colour-tint of its own which gives the final reaction a mauve shade. In this case it is necessary to use a four-chambered comparator. In two chambers are placed, one behind the other, a tube containing urine plus reagent and a second tube containing water. In the two other chambers are placed a standard tube and another containing cleared urine but without the addition of reagent. It should be possible to obtain matching of equal tint and intensity between the two sides.

Results.

When this method is applied to urine from young healthy infants, receiving human milk or artificial feeds which are well balanced and sufficiently rich in vitamin C, the figure generally obtained is at least 8 U.H. It is from this fact that an attempt was made to detemine the requirements of vitamin C for healthy infants in the early months of life by substituting, during two periods of twenty-four hours, a diet strictly free from vitamin C for their usual food. Surprisingly it was found that in contrast to what occurs in older children and in adults, the intensity of the reaction, instead of falling to zero, was increased in infants between two and nine months. Between the ages of nine and eleven months there was a certain variability. In one of the two infants in this group the elimination of vitamin C increased during the second day of the experiment. This infant behaved, therefore, like those of the younger age period. In the other infant, the figure for U.H. fell towards the end of the second day. With infants over one year in age (fourteen to thirty-three months) the elimination of vitamin C fell to zero by the end of the first day or at the latest by the end of the second or beginning of the third day[3].

These experiments have shown for the first time in a strict sense that the healthy and normal human infant is capable of synthesizing vitamin C. This function tends to decrease towards the eleventh month and is definitely lost after the end of the first year. In later experiments it has been shown that the synthesis of vitamin C is carried out physiologically by the infant independent of the vitamin C taken in with the food. The quantities of this vitamin which are utilized, in fact, appear greatly to exceed the amounts taken into the body even under the best conditions. For example, an infant of fifteen days ingested 2,990 U.H. in twenty-four hours and excreted 6,050 U.H. Another, aged two months, took in 2,400 U.H. in twenty-four hours and passed out 6,496 U.H. A third, aged two months, ingested on the first occasion 1,990 U.H. and excreted 3,288 U.H. Four days later the figures were 470 and 4,638 U.H. respectively. This case is a fine example of the fact that the ' consumption ' of vitamin C greatly exceeds the quantity of this substance available in the food of the young infant and that it remains the same whatever the vitamin C content of the diet. If the food contains little of the vitamin, the infant's body produces a greater quantity.

By further experiments it has been shown that the same synthesis of vitamin C is going on in the case of the milch cow and that the vitamin C content of the milk is independent of the cow's food intake. It is well recognized that summer milk is richer in vitamin C than winter milk and this

difference is not entirely due to variations in the vitamin C content of the diet (Florence, Macleod). The synthesis of vitamin C by the milch cow had already also been demonstrated in guinea-pig tests by Hughes, Fitch, Cave and Riddell[4]. It has been shown by us[5] by the colorimetric method, which allows much more frequent estimations, that there exists in the milch cow an annual cycle in the sense that the vitamin C content of the milk remains low during the winter, and goes up sharply in March, well before the grazing season and at a period when the feed of the animals has not yet undergone any essential change. The vitamin C content remains high until November when it falls abruptly to the winter level which does not vary until March.

There are, therefore, extra-alimentary factors which regulate the vitamin C content of the milk. It is only possible to put forward suppositions as to their nature: solar radiations, temperature, certain cyclical hormonal influences can be taken into consideration.

Discussion.

To return to the pathogenesis of scorbutic dystrophy it will be seen, in the light of the experiments just quoted, that it is no longer possible to maintain the theory which explains its occurrence by the simple lack of vitamin C in the infant's diet. The infant does not become scorbutic because his food is lacking in vitamin C, but because the inherent function controlling the synthesis of this vitamin has become feeble or has disappeared. This fact also explains the capricious and irregular manner in which this disorder occurs in the infant. The problem therefore arises to to what are the conditions governing the total or partial inhibition of the synthesis of vitamin C in the infant. A priori, two possibilities must be considered: the infant's diet might be lacking in the dietetic factors from which the synthesis of ascorbic acid takes place or even this function itself could be diminished or completely inhibited by some pathological influence.

The former of these possibilities must first be faced. It definitely occurs under certain conditions. It is well-known that vitamin C itself is not stored in the body. In animals unable to manufacture it or in man from the second year onwards it only requires the elimination of the vitamin from the diet for two days to produce complete disappearance of the urinary excretion of the vitamin. It has been shown that the human infant, during the first year of life, is independent of the dietetic supply of vitamin C since he can manufacture it for himself. Consequently it was surprising to find in infants aged from one to eight months, fed on a commercial milk preparation, that the urinary elimination of vitamin C disappeared after four to five days of this diet. The preparation used was particularly poor in vitamin C, but the infants, who were healthy, should have been able to compensate for this deficiency by an increase in their production of the vitamin. It must therefore be admitted that this particular food is lacking in a substance which contributes to the synthesis of vitamin C.

Does it lack a ' provitamin '? This is not probable for the following reasons. It is difficult at present to be precise about the unstable bodies which form the steps in the synthesis of the vitamin. It can, however, be said that 2-keto-gulonic (or *l*-sorburonic) acid and 2-keto-galactonic acid

appear to be the only stable and sufficiently characterized precursors which precede the formation of vitamin C. It is probable that these substances play the part of ' provitamin C.' It is not yet proved that these acids or in general the substances designated as ' provitamin C ' are normally present in the food and in the tissues of the higher animals, but there is nothing chemically to oppose the view that these bodies can be formed by biological processes from material which is widely distributed in living matter. This is the reason why it is necessary to accept that it is not the lack of ' provitamin C ' which appears to be the dominant cause of the cessation of the synthesis of vitamin C in the animal.

This synthesis is, in fact, still controlled by other factors which are necessary to produce the passage—difficult from the chemical point of view—of the provitamin to the vitamin. Waldmann has recently shown[6] that the urine of rats and birds ceased to give the violet reaction of Bezssonoff when these animals (who are manufacturers of vitamin C) are submitted for several days to a diet of decorticized rice. If bran or yeast is added to the diet, the reaction reappears but it remains indefinite and abnormally feeble. If the further addition is made of cod-liver oil, the reaction is greatly intensified and becomes normal. If the diet of decorticized rice is supplemented only by cod-liver oil the violet reaction does not appear.

The interest of these findings lies in the demonstration that vitamins A and D and probably the vitamin B complex, have a decisive action upon the biological synthesis of vitamin C. Our own researches have independently confirmed those of Waldmann, namely that the intake of fat-soluble vitamins plays a definite part in the accomplishment of the synthesis of ascorbic acid in the animal body.

In the infants mentioned above the intake of vitamins A and D was augmented without changing the amount of vitamin C in the diet. Five of the nine infants were each given half of the yolk of a raw egg daily, to the four remaining infants there was given 0·03 c.c. of an extract of fish oil, representing in vitamins A and D, the equivalent of about 1·2 c.c. of a good cod-liver oil. After seven days of this treatment the urinary excretion of vitamin C reappeared in four infants of the former group and, after eight days, in all the infants of the second group. The intensity of the violet reaction in the urines was, respectively, 8, 7, 6, 4, 4, 4, 3 and 2 U.H. Thus the addition of fat-soluble vitamins to a diet lacking in vitamin C re-established the synthesis of this vitamin in the infant's body in eight out of nine instances. Certain considerations permit the view that the action of vitamin A predominates in this connection, since according to H. de Euler[7] the biological evolution of this vitamin is related to that of vitamin C. This is, moreover, a point which it will not be difficult to verify experimentally.

From these observations it may be concluded that even if the healthy infant is, during the early months of life, independent of the supply of vitamin C in the diet because he is able to synthesize it for himself, the quality of the diet cannot altogether be ignored. This must be well balanced: the lack of other vitamins, and in particular vitamin A, can lead to a diminution of the synthesis of vitamin C and thus take part in the pathogenesis of scorbutic dystrophy.

The second possibility for explaining the etiology of scorbutic dystrophy is that the synthesis of vitamin C is inhibited as a result of a pathological condition. Such a condition ought to show itself in infants maintained on a rational diet by the disappearance of the violet reaction in the urine. Our experience has shown that this is quite a frequent happening.

It must first be recalled that vitamin C deficiency shows itself in the older child and in adults simply by the disappearance of the violet reaction. In these cases if the urine is examined by means of the monomolybdophosphotungstic reagent there is no reaction. It is interesting to note that this simple absence of reaction is uncommon in the young infant. We have only observed it twice and only transitorily in some thousands of analyses. At this age the disappearance of the violet reaction is invariably followed by pathological reactions, showing themselves either by a yellowish brown colour or by the formation of a whiteish-grey precipitate (' cloudy reaction '), the supernatant liquid remaining colourless. Sometimes a mauve tint is obtained which, when it is not due to the yellow colour of the urine, results from a super-imposition of yellow and violet (' mixed reaction '). Observation of a large number of cases has shown that the yellow reaction is always the index of a pathological process. From the chemical point of view it is difficult to explain for there are many substances which might produce it. Thus this reaction can be obtained with pyrogallol, with tannin and especially with different alkaloids: it is accompanied by the formation of a precipitate when the concentration of the alkaloid reaches a certain limit. Skatole gives a yellow reaction when its concentration reaches 10 mgm. per litre. In greater concentration (above 100 mgm. per litre) a precipitate occurs in an acid medium in the presence of excess of the reagent: a reddish-brown precipitate is formed by four to five molecule of diskatole with one molecule of reagent and the supernatant liquid is coloured violet.

The ' cloudy reaction ' is, in general, due to the fact that very different nitrogenous bases form complex combinations with the reagent, which are only slightly soluble. Cretinine is precipitated in the presence of the reagent when its concentration reaches 320 mgm. per litre. Precipitation of guanine occurs when its concentration in distilled water approaches saturation (at 20° C.). The precipitation of skatole has already been mentioned. The cloudy reaction is readily observed in the adult following a diet rich in meat, for example. It is present only in pathological cases in infants. Its significance remains doubtful. It is possible that it indicates the complete disappearance of vitamin C, involving, in infants who are very sensitive to this deficiency, a disturbance of nitrogenous metabolism showing itself by the excretion of substances which produce the yellow or the cloudy reaction. But it is also possible that there exist combinations of these substances with ascorbic acid and that the pathological reactions only indicate the absence of free ascorbic acid from the urine, showing that the quantity of vitamin C prepared by the body is insufficient in the presence of an exaggerated pathological requirements. It can therefore be asserted that the disappearance of the violet reaction in the urine and the appearance of one of the other reactions, always represents a certain degree of vitamin C deficiency.

Clinical results.

To determine the frequency of deficiency states in young infants, investigations have been carried out on two hundred and forty-six children in the hospital. Amongst these, healthy infants or those who could be regarded as such at the end of their convalescence were naturally exceptional.

Amongst the latter the violet reaction was the rule, being found in one hundred and ten instances. Among the infants suffering from a chronic disease process the yellow reaction was found in one hundred and thirty-six instances. To determine the distribution of the two reactions among the infants admitted to the department for whatever reason, fifty-eight unselected children have been examined, all of whom were receiving a normal and balanced diet. The violet reaction was found eleven times and the yellow reaction forty-seven times.

In order to study more closely the distribution of the different pathological reactions in relation to the disorders of the infants, the one hundred and twelve patients who did not give the violet reaction have been utilized. The yellow reaction was given by seventy-eight of these cases, the mixed reaction by seven, the cloudy reaction by twenty-six and a negative result by one. This last infant had lost the violet reaction the day before and by next day the urine gave a yellow reaction. As a general rule it was found that the yellow reaction was obtained in infants with chronic disease, in premature infants, in those designated as dystrophic, hypoarthrepsic, and hypotrophic, in dyspeptic conditions, in coeliac disease, in habitual vomiting and in pyloric stenosis, in rickets and spasmophilia, in anaemia, eczema, tuberculosis, the non-febrile stages of whooping cough and various other chronic wasting affections. In rare instances a mixed reaction was obtained. The cloudy reaction appeared principally and regularly in infections. Very often the appearance of this reaction allowed the prediction of the onset of an infectious disorder which appeared later.

Conclusions.

Our investigations have reached this point. They show that with the aid of the reaction with monomolybdo-phosphotungstic acid it is possible to detect states of deficiency in vitamin C at a stage when they do not show themselves by any other characteristic sign. On the one hand, this method permits the study of the conditions under which the synthesis of vitamin C in the infant's body is inhibited and allows the following up from the onset of the repercussions of the vitamin C deficiency on the organism. On the other hand, the disappearance of the violet reaction and the appearance of the yellow reaction indicate the moment when it is necessary to begin the administration of vitamin C, which should be increased until the appearance of the violet reaction in the urine and continued as long as this reaction shows any tendency to become feeble or to disappear. There is thus available a simple method by which in the future the occurrence of scorbutic dystrophy can be prevented.

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STUDIES IN THE ANAEMIA OF INFANCY AND EARLY CHILDHOOD

Part X.—The anaemia of infantile scurvy

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Although every writer on infantile scurvy comments on the characteristic changes in the complexion of the patient, stressing the development of a sallow muddy tint and, in advanced cases, of pallor, the occurrence of actual anaemia is not so universally accepted; further, the existence of a special form of anaemia due to absence or deficiency of ascorbic acid (vitamin C), and only curable when that vitamin is administered in efficient amounts, is a modern conception which still awaits general recognition. Nevertheless a perusal of Barlow's[1] two classical papers shows that he was under no misapprehension as to the presence of anaemia and his comments on this symptom are illuminating; in his first paper he writes : ' The anaemia in severe cases was profound, besides the pallor there was noted sometimes a peculiar sallow muddy tint on the complexion,' and in his second paper the point is further elaborated :

' With respect to the constitutional symptoms . . . the most important is the profound anaemia which is developed. Whatever there may have been at the onset when once the limb affection has become pronounced the pallor becomes intensified. The anaemia is proportional to the amount of limb involvement. As the case proceeds there is a certain earthy-coloured or sallow tint which is noteworthy in severe cases, and when once this is established bruise-like ecchymoses may appear and more rarely small purpurae.'

An interesting contrast to these statements is found in a recent article written by Barlow's most distinguished pupil. ' The blood shows no characteristic change in its cell count. A simple secondary anaemia with diminution especially of haemoglobin has been found in some cases; but this is not always so, the writer has found the number of red cells rather above the normal in some pronounced cases of scurvy ' (Still[2]).

Quotations from many writers could be given for and against the view that anaemia is frequent in scurvy; indeed some authors regard the

pallor of scurvy as due to circulatory changes in the skin and not the result of anaemia. Barlow thought that the muddy tint of the complexion was due to the absorption of altered haemoglobin, but since a similar tint is sometimes seen in erythronoclastic anaemias, agranulocytic angina, and even in acute osteomyelitis it is also possible that it is an indication of some injury to the bone marrow; moreover it has been found that in scurvy neither this tint nor the pallor is indicative of the severity or even of the presence of anaemia. For instance, a child (case 5) suffering from severe scurvy (as shown by the presence of scorbutic gingivitis, swelling of legs with pseudoparesis, orbital haemorrhage, recession of sternum and cartilaginous ribs, 15–20 red cells in the uncentrifugalized urine per high power field), although markedly pale presented a normal blood picture, the red cells being $5\frac{1}{2}$ millions per cubic millimetre and the haemoglobin 98 per cent. In 1932 Rohmer and Bindschedler[3] published a paper recording the results of an examination of the blood in fifteen cases of infantile scurvy seen during the preceding five years. They found anaemia in only seven instances and came to the conclusion that anaemia could not be regarded as a constant and essential symptom of scurvy, but considered that its appearance was probably connected with certain super-added conditions which did not form part of the picture of uncomplicated scurvy. Baar[4] found anaemia in only one-third of his cases; Shipley[5], on the other hand, found a degree of anaemia in every case of his series. These results suggest that anaemia is far less common in scorbutic infants than in scorbutic adults, because in the latter 70-80 per cent. of the recorded cases whose blood has been examined, have been found to have anaemia of severe or moderate degree[6].

The blood in scurvy.

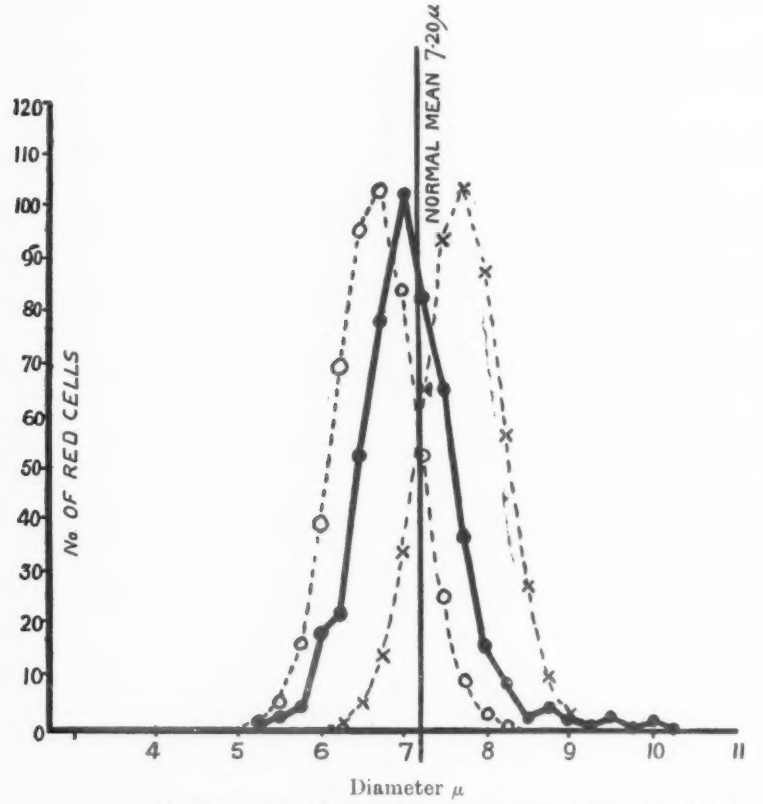
Frank scurvy is nowadays a rare disease and in the last three years we have only been able to study six cases by modern haematological methods, yet these have been sufficient to demonstrate conclusively both that severe scurvy may occur without any evidence of anaemia and that scurvy may be associated with an anaemia which is solely the result of a deficient supply of vitamin C. The anaemia is in fact a characteristic symptom of scurvy, but just as every case, even of severe scurvy, does not present the whole gamut of the scorbutic syndrome, so sometimes anaemia occurs and sometimes the blood is normal. The results obtained in our series are set out in table 1, a reference to which shows that anaemia was present in four cases but only reached a severe degree in one case (case 1). This child had a red cell count of 2,310,000 per c.mm. and haemoglobin 35 per cent., giving a colour index of 0.76, and actually during the stay in hospital the colour index at one time was as low as 0.6. Shipley[5] has reported even lower haemoglobin figures, for instance a 29 per cent. haemoglobin with a red cell count of 2,480,000 per c.mm. The anaemia is either orthochromic or hypochromic. The red cells show ring staining when the colour index is low and may show a moderate degree of anisocytosis. Three of the four cases showing anaemia were investigated

TABLE 1.

Case	Date	Red corpuscles per c.mm.	Haemoglobin per cent.	Colour index	Volume index	Saturation index	Mean red cell diameter μ	Standard deviation μ	Coefficient of variation per cent.	Reticulocytes per cent.	Nucleated reds per c.mm.
1. J. R., aet 9 mth.	24.3.32	2,310,000	35	0·76			7·009	0·688	9·82	2·0	100
	29.3.32	3,276,000	41	0·62			7·065	0·604	8·54	7·5	2,250
2. A. L., aet 9 mth.	14.9.34	4,190,000	69	0·82	0·87	0·95	7·284	0·611	8·39	0·8	
3. J. H., aet 10 mth.	14.9.34	3,990,000	70	0·87	0·98	0·90	7·186	0·518	7·21	0·2	
4. B. M., aet 8 mth.	21.7.33	5,130,000	82	0·80	0·82	0·96				0·2	
5. G. G., aet 11 mth.	14.11.34	5,500,000	98	0·89	0·98	0·92	7·128	0·480	6·73	1·1	
6. J. F., aet 9 mth.	22.5.33	4,530,000	98	1·08	1·08	1·01				0·2	

by means of Price-Jones' curve, and in each case the cells were of normal average diameter (see fig. 1). In two of these anisocytosis of moderate degree was present as shown by a high coefficient of variability, i.e., 8.54 and 8.93 per cent., the normal limits according to Price-Jones being 5.64 to 7.26 per cent. (see fig. 1).

FIG. 1.



o - - - - - o Ideal curve for the smallest (— 3σ) mean diameter (6·686μ) within normal limits

× - - - - × Ideal curve for the largest (+ 3σ) mean diameter (7·718μ within normal limits

●——● Red cell diameter distribution curve in a case of severe anaemia of scurvy (case 1 J.R. 29.3.33)

M.D. 7·065 μ
σ 0·604 μ
v 8·54 per cent.

The microhaematocrit method as devised by our colleague, the late R. J. Gittins, is, in our opinion, the best clinical method for estimating the average size of the red cells, and this gave a volume index (the mean volume of a single cell relative to normal) under 0.9 in two cases, indicating a slight degree of microcytosis such as is found in the mild 'secondary' anaemias of infective origin or those resulting from small haemorrhages. The saturation index (the mean corpuscular haemoglobin concentration relative to normal) revealed normal packing of the red cells with haemoglobin. The bleeding and clotting times and clot retrac-

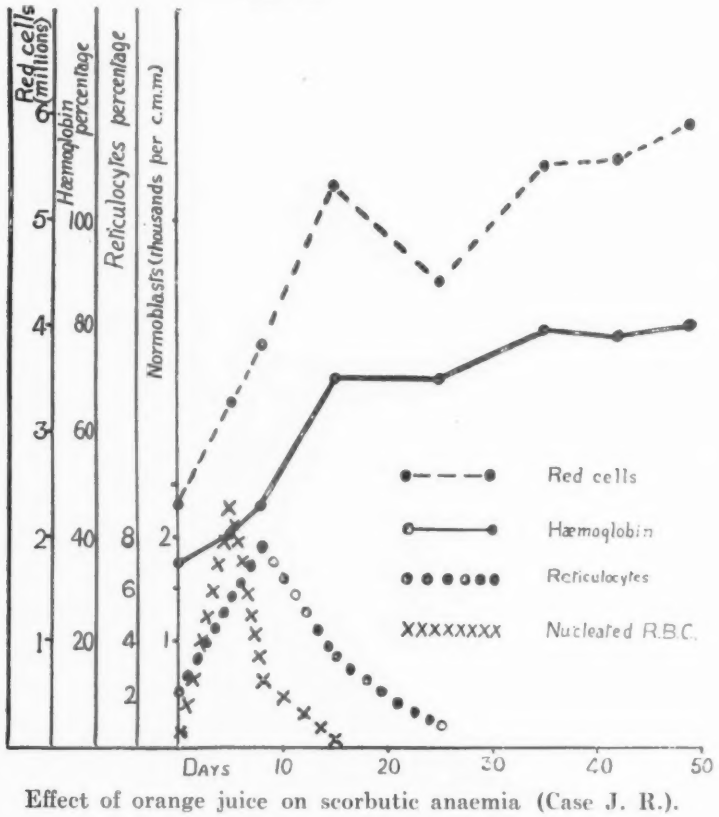
tion were all normal, and there was no diminution in the number of blood platelets. The differential white cell count showed no constant change. In two cases (3 and 6) a lymphocytosis (77 per cent. and 68 per cent. respectively) was present. A polymorphonuclear leucocytosis may occur owing to the presence of an infection, a not improbable complication since, to borrow a simile from Shipley the incidence of an infection not infrequently fans the embers of a latent scurvy into the intense flame of an acute attack.

As in nutritional anaemia the occurrence of an infection may also be a factor in increasing the anaemia of the scorbutic infant, and further, in the long-standing cases (which provide the most outstanding examples of anaemia), the effect of repeated haemorrhage is added to the original scorbutic blood picture, and the anaemia may then become hypochromic. In the quotation from Barlow's paper already given it is stated that the pallor became intensified when limb involvement was pronounced and was proportional to the amount of limb involvement. It seems reasonable to suppose that this may have been the result of large sub-periosteal haemorrhages. For instance, the child already referred to (case 1), had suffered from pseudo-paralysis for a period of two months before coming to hospital but only became pale shortly before admission thereto. She had large sub-periosteal haemorrhages and a severe hypochromic anaemia which became even more hypochromic shortly after admission, an occurrence which seems to be added proof of the effect on the blood of recent large haemorrhages.

The fact that there is a true anaemia of scurvy, the result of a specific deficiency, and that this deficiency is of vitamin C, is shown by the effect of treatment since all the cases responded rapidly both haematologically and clinically to treatment with orange juice. In all our observations on the deficiency anaemias of childhood we have adopted a method whereby the child is kept on the diet on which the anaemia has developed and then the factor which it is considered may be deficient, e.g., iron, is added. If after a short period a reticulocytosis, together with an improvement in the anaemia, does not take place, some other factor, e.g., copper, is tried, and so on. If a partial improvement only occurs the effect of a combination of factors, e.g., iron, copper and yeast, is tried. The most striking result of treatment with vitamin C is shown in case 1 (see fig. 2). This child, aged nine months was fed on milk. When orange juice was added a brisk reticulocytosis occurred, reaching its maximum on the eighth day, and on the fifteenth day the red cells were normal in number, having been more than doubled, and the haemoglobin had increased from 35 to 70 per cent. The anaemia eventually progressed to a complete cure. The increase in the nucleated red cells following the onset of treatment was interesting and may be regarded as the result of normoblastic proliferation in the bone marrow. Incidentally it is perhaps worthy of note that both

iron and liver preparations free from iron and vitamin C have been proved to be useless in the treatment of scorbutic anaemia in adults[6].

FIG. 2.



Effect of orange juice on scorbutic anaemia (Case J. R.).

The blood in latent scurvy.

The occurrence of a condition which has been called latent or sub-scurvy has been challenged by some authorities and it must be admitted that proof of its existence has hitherto been lacking; nevertheless, on first principles it does seem feasible that if frank scurvy is the result of a grossly defective vitamin C intake, less severe defects should produce a condition of affairs predisposing to the onset of acute manifestations. In other words the deficiency in vitamin C does not produce an ' all or nothing response '; indeed the influence of infection in determining the onset of acute scurvy can only be adequately explained by such a conception. Incidentally, as pointed out by L. J. Harris and Ray[7], it may be that in future we shall be able to recognize latent scurvy by the estimation of ascorbic acid in the urine, and particularly by the effect of the oral administration of ascorbic acid on its urinary output. The question whether anaemia may occur as the result of latent scurvy has been raised by some writers, and in 1922 Weill and Mouriquand[8] described a form of anaemia in infants which resisted treatment by iron but was cured by the administration of lemon juice. Ten years later Rohmer and Bindschelder[3] published the results of an investigation of a group of twenty-two anaemic infants; in six of these children the anaemia was unaffected by the administration of iron, but when vitamin C was given in addition to iron a prompt cure resulted.

These authors suggest that vitamin C may have some effect on the metabolism of iron, but it is much more probable that these cases were instances of deficiency anaemia due to the absence of more than one factor, since it is not unusual for a diet which is defective in one essential to be defective in others also. Hence it is quite conceivable that a child who has nutritional anaemia may develop scurvy and the anaemia of scurvy and that therefore for its complete cure both iron and vitamin C would be required, although it must be admitted that those occasional cases of nutritional anaemia which in our experience have proved resistant to iron have never shown any haematological improvement as the result of intensive vitamin C therapy.

Maturation of the red cell.

In his various communications on anaemia Witts[9] has set out a scheme showing how the maturation of the red cell depends on the supply to the bone marrow of certain building materials; thus the haematinic factor produced by the interaction of intrinsic factor in the gastric juice with the extrinsic factor in the diet is necessary to ensure the maturation from the megaloblast to the normoblast, and for the maturation from the normoblast to the erythrocyte he postulates the necessity for iron, copper, vitamin C and thyroxin. Further, in the event of the absence of any of these factors, anaemia having certain characteristics develops, and according to the level at which haemopoiesis is arrested the marrow is megaloblastic or normoblastic. Thus in the absence of the haematinic factor the bone marrow becomes hyperplastic and megaloblastic and a megalocytic hyperchromic anaemia results. In the absence of iron or copper or vitamin C or thyroxin the bone marrow becomes hyperplastic and normoblastic, a microcytic anaemia resulting. Whilst this is a simple and attractive scheme it does not tell the whole story and in our opinion may not be entirely correct; for instance, haemin is an iron porphyrin, and porphyrin is made up of a number of five-ring carbon compounds (the pyrrol ring) which cannot be synthesized in the body. Therefore substances containing the pyrrol ring are necessary for the maturation of the red cell, and incidentally this may furnish a partial explanation of the beneficial effect of yeast in some forms of anaemia and also of the proprietary compound Phyllosan, since both these contain porphyrins (cytochrome and chlorophyll respectively). Again it is probable that one of the factors necessary for the budding of the reticulo-endothelial cells to form the haemangioblast which in turn become the megaloblast is an anoxaemia; possibly also there may be an unknown specific food factor responsible for this step, in the absence of which an aplastic anaemia occurs. The existence of such an unknown factor is envisaged by Witts in his last communication. Finally, it has already been stated in this paper that the anaemia of scurvy is usually normocytic and orthochromic; certainly it cannot be called microcytic in the sense that iron deficiency anaemias are microcytic.

We have never been able to understand Witt's view that when red cell maturation is held up at the level of normoblastic development the

resulting erythrocytes must necessarily be microcytic. None of the normoblasts that we have been able to measure in blood films and smears of bone marrow stained with the usual blood stains has been obviously smaller than the red cells present in those preparations; in fact many of them (frequently classified as macronormoblasts) have a diameter larger than normal. With the exception of certain of the congenital dystrophies of the erythron such as acholuric jaundice in which the red cells are more globular or fatter than normal, definite microcytosis is only found in two groups of blood disease. The first includes those anaemias of which pernicious anaemia is the outstanding example, in which poikilocytosis is prominent, and the microcytosis is probably the result of excessive cell fragmentation. The second group is that of the iron deficiency anaemias, which includes the nutritional anaemia of infancy, the idiopathic hypochromic anaemia of middle life, the hypochromic anaemia of coeliac disease and the anaemia of chronic haemorrhage. In all the anaemias of this group there is a disproportionate reduction of haemoglobin so that the colour index is low, and the microcytosis may be explained as an adjustment on the part of the body and its red cell factories to ensure the best utilization and distribution of the available haemoglobin, since, by packeting this in relatively large numbers of smaller cells a more extensive surface area for oxygen exchange is provided.

Bone marrow in scurvy.

A study of the bone marrow in scurvy is important in determining the action of vitamin C in the maturation of the red blood cell.

References in the literature on this point are scanty, but MacCallum[10], Naegeli[11], Shipley[5], Holt and McIntosh[12] all describe a disappearance of the blood-forming tissues from the marrow and their replacement by fibrous tissue. Mettier, Minot and Townsend described the bone marrow as moderately hyperplastic and it is on their work that Witts bases his views on red cell maturation in scurvy. These observers studied two specimens of bone marrow taken from the sternum of one of their adult patients who showed scorbutic anaemia, the first before the commencement of treatment, and the second at the height of the reticulocytosis which occurred after giving orange juice. Concerning the first specimen (before treatment) they say, 'The tissue shows moderate cellular hyperplasia and contains a few isolated fat cells. There are scattered, small, varying sized groups of nucleated red blood cells . . . There is no evidence of fibrosis.' On the other hand in the second specimen (showing the result of treatment) they found 'Quantitatively more nucleated red blood cells. Mitotic figures among the precursors of these cells were not apparent in the specimen obtained from the patient prior to any treatment whereas in the specimen obtained at the time of the peak of the reticulocyte rise, a few mitotic figures appear in each field of the microscope.' As a result of their study of these two specimens they suggest that vitamin C 'can promote in some fashion the development of nucleated erythrocytes,' and conclude that 'in scurvy and in anaemias responding to iron perhaps the effective substance hastens maturation of normoblasts.'

It appears to us, however, that this picture of increased numbers of normoblasts actively dividing is an indication of greater production rather than maturation of these marrow elements. The best description of the

scorbutic bone marrow that we have found is in a paper by H. A. Harris[13], in which he gives a detailed account of the bones and bone marrow obtained at post-mortem from a case of scurvy. He describes the manifestations of scurvy as consisting of areas of haemorrhage, areas of excessive development of fibrous tissue, and areas of gelatinous marrow devoid of blood-forming cells, and concludes that ' anaemia in scurvy is not only due to the succession of haemorrhages but is due to the formation of gelatinous marrow with failure of differentiation of the marrow into erythroblastic and leucoblastic areas.' His specimens showed some healing of the scorbutic process at the bone ends in contiguity with the epiphyseal line, and in this situation a few normal marrow cells were seen which he regards as a clear indication that ' the process of healing is not dependent on extension of the normal tissue but on a special differentiation in situ as a result of blood-borne substances.' These findings, which represent the investigations of the whole bone and are in accord with the findings of MacCallum, Naegeli, Shipley, Holt and McIntosh, probably represent a truer account of the state of the marrow in scurvy than that quoted above of the examination of small samples of sternal marrow obtained by biopsy which cannot claim justly to represent changes present throughout the whole erythropoietic system. Nevertheless it is well known that hyperplasia is frequently followed by degeneration and aplasia, especially in bone marrow, and the findings reported by Mettier and his colleague may quite possibly represent a stage prior to a gelatinous degeneration.

The maturation of the red cell in scurvy.

Vitamin C probably functions in the body by forming an oxidation-reduction system, taking up oxygen in the tissues, and subsequently by its power of reversible oxidation functioning as an oxygen carrier and thereby playing an important part in the processes of tissue respiration and metabolism. Confirmation of this theory exists in two sets of experiments. First the work of Harrison[14] and of Euler and Klussmann[15], who have shown that slices of the fresh tissues of scorbutic animals have a low oxygen uptake which is restored by the addition of ascorbic acid; secondly that of Söderström and Törnblom[16] who have shown that in scurvy in animals the oxygen consumption is lowered. It seems probable, therefore, that like thyroxin, vitamin C is responsible for cell metabolism and that its action upon the cells of the bone marrow is throughout the whole range of maturation from endothelial cell to adult erythrocyte and not restricted to the stage of maturation of the normoblast, as suggested by Witts.

In our opinion the anaemia of scurvy results from a general slowing down of the whole process of erythropoiesis which may be so marked as to result in marrow degeneration and aplasia, the resulting anaemia being therefore usually orthochromic and normocytic; in chronic cases associated with large haemorrhages into the tissues and from mucous membranes a post-haemorrhagic blood picture becomes superimposed and the anaemia may then become hypochromic and it is conceivable that in extreme cases it might even become truly microcytic. On this hypothesis it might be

expected that a megalocytic anaemia should occur at times the result of a disproportionate slowing up of red cell development at the stage of maturation of megaloblast to normoblast. We have not observed this but Mettier, Minot and Townsend say of the red cells in adult scurvy that ' occasionally there may be a sufficient number of nonachromic cells slightly larger than normal to suggest the possibility of pernicious anaemia.' Unfortunately these workers did not estimate the size of the red cells, but this description is of blood films from untreated cases in which ' about one per cent. of the cells are usually polychromatophilic.' It is clear, therefore, that these larger cells were not reticulocytes and the description almost warrants the assumption that a megalocytic blood picture does occur in scurvy*.

The rôles played by vitamin C and thyroxin in the maturation of the red cell are in our opinion very similar since the anaemia of cretinism in our experience is also usually orthochromic and normocytic, occasionally macrocytic and never microcytic.

Conclusions.

1. Anaemia is a characteristic but not invariable symptom of infantile scurvy.

2. The anaemia of infantile scurvy is due to a deficiency in vitamin C and is cured by its administration in adequate quantities.

3. The anaemia of infantile scurvy is usually orthochromic and normocytic, microcytosis if present is slight in degree and cannot be compared with that present in the iron deficiency anaemias.

4. Reasons are given for the belief that vitamin C is required in all stages of maturation of the red cell from the reticuloendothelial cell to the erythrocyte.

We wish to place on record our grateful thanks to the Medical Research Council for defraying the expenses of our research work on the anaem as of childhood.

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* Since this paper was written we have observed an example of macrocytic anaemia in infantile scurvy. (L. G. P. and W. C. S.)